CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205834Orig1s007, s008, s009

MEDICAL REVIEW(S)

CLINICAL REVIEW

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Division / Office	DAVP/OAP
Reviewer Name	Charu Mullick, MD
Review Completion Date	January 27, 2016
Established Name	Ledipasvir/sofosbuvir (LDV/SOF) fixed dose combination
Trade Name	Harvoni®
Therapeutic Class	HCV direct acting antiviral; NS5A inhibitor (LDV), NS5B polymerase inhibitor (SOF)
Applicant	Gilead Sciences, Inc.
Formulation	Tablet 90 mg LDV/400 mg SOF
Dosing Regimen	One tablet taken orally once daily
Indication	Treatment of chronic hepatitis C
Intended Populations	Adults with 1) decompensated liver disease, regardless of liver transplantation status, and 2) liver transplant recipients with compensated liver disease

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend ledipasvir/sofosbuvir (LDV/SOF) with ribavirin (RBV) for 12 weeks for the treatment of chronic hepatitis C (CHC) infection in adults with decompensated liver disease, and post-liver transplant recipients with compensated or decompensated liver disease. The recommendations are based on data from two phase 2 trials, GS-US-337-0123 and GS-US-337-0124 (also known as SOLAR-1 and SOLAR-2) submitted in the NDA supplements 007-009.

Ledipasvir/sofosbuvir, 90 mg/400 mg, taken once daily was approved previously for genotypes 1, 4, 5, 6 CHC patients with compensated cirrhosis or without cirrhosis. The SOLAR-1 and 2 trials evaluated the safety and efficacy of LDV/SOF with RBV administered for either 12 weeks or 24 weeks in 670 subjects with genotype 1 or 4 CHC with decompensated liver disease as well as post-liver transplant recipients.

The risk benefit assessment is favorable and supports an approval recommendation for LDV/SOF plus RBV for 12 weeks for patients with:

- Decompensated cirrhosis genotype 1,
- Post-liver transplant patients with decompensated cirrhosis genotype 1,
- Post-liver transplant patients without cirrhosis or with compensated cirrhosis genotypes 1 or 4.

In the SOLAR-1 and 2 trials, the 12 week regimen of LDV/SOF with RBV was reasonably well-tolerated. Efficacy was assessed as the proportion of subjects attaining sustained virologic response at posttreatment week 12 (SVR12), an accepted benchmark of HCV virologic cure. Based on SVR12 and virologic relapse rates, the 12 week treatment duration of LDV/SOF plus RBV was selected for the proposed populations. The lack or limited available medical therapy for CHC in patients with decompensated liver disease and post-liver transplant patients, respectively, is recognized. In general, virologic cure defined as achieving SVR12 has been shown to result in the histologic improvement of fibrosis, reduced progression of fibrosis, reduced mortality, and improved quality of life in various populations. The risk benefit assessment also takes into consideration the estimated one-year mortality rate ranging from 20% to 50% in untreated decompensated cirrhotic patients who are unable to receive liver transplantation.

No new formulation is proposed; both LDV/SOF FDC and RBV are previously approved agents. No issues were identified in clinical site inspections to preclude approval.

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1.2 Risk Benefit Assessment

The overall risk benefit assessment is favorable for the 12 week regimen of LDV/SOF with RBV for the treatment of genotype 1 CHC patients with decompensated cirrhosis. The overall risk benefit assessment for the 12 week LDV/SOF with RBV is also favorable for treatment of post-liver transplant patients with compensated (genotype 1 or 4) or decompensated cirrhosis (genotype 1). The assessments are based on review of data in the above-stated populations in two phase 2 trials, SOLAR-1 and SOLAR-2, and also taking into account the current context of disease including lack or limited alternative medical therapies available to such patients. No dose adjustment is needed for LDV/SOF or RBV in the setting of hepatic impairment. In addition, there are no unique drug-drug interactions with immunosuppressive agents to require restricted use in posttransplant patients. To summarize, the benefits of hepatitis C virologic cure are outweighed by the expected risks with LDV/SOF plus RBV in patients with decompensated cirrhosis and in posttransplant patients.

Risks

In SOLAR-1 and 2 trials, LDV/SOF plus RBV for 12 weeks was reasonably well-tolerated, even in subjects with decompensated cirrhosis with greater comorbidities and advanced liver disease. In the 12 week treatment arms, LDV/SOF was well tolerated with few discontinuations (1%). With RBV, the primary toxicity was anemia which was managed with dose reduction, supportive therapies including iron supplements, and blood transfusions. Ribavirin was discontinued in 8% and 14% of subjects with compensated and decompensated liver disease, respectively. Overall, RBV-induced anemia is a toxicity which can be adequately managed with periodic monitoring of hemoglobin, RBV dose adjustment and other supportive therapy. Symptomatic bradycardia identified previously with SOF-containing regimens coadministered with amiodarone is labeled in the LDV/SOF package insert in Warnings and Precautions. An increased risk or a new trend in bradycardia was not identified in the SOLAR-1 and 2 trial populations.

Benefits

Subjects with decompensated cirrhosis irrespective of transplant – genotype 1
Presently, there is no approved medical therapy for CHC patients with decompensated liver disease, and patients ultimately progress to liver failure and death. Without liver transplantation, patients with decompensated cirrhosis CPT B and CPT C are estimated to have a one-year mortality rate of 20% and 50%, respectively. In the U.S., the organs available for transplantation annually are outnumbered by the patients enlisted for transplantation.

In the SOLAR trials, SVR12 response in pre-transplant genotype 1 patients with decompensated cirrhosis (CPT B and C) was 87% and 89% with 12 weeks and 24

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weeks of LDV/SOF plus RBV, respectively. In posttransplant genotype 1 patients with decompensated cirrhosis CPT B, the SVR12 response was 89% and 96% with 12 weeks and 24 weeks LDV/SOF plus RBV, respectively. In these groups, the primary reasons for not attaining SVR12 were death or virologic relapse. Virologic relapse occurred in 7% and 4% of subjects with 12 week and 24 week treatment, respectively. Subgroup analysis did not identify consistent trends in any subgroup to justify the longer 24 week treatment compared to 12 weeks of treatment; and the 12 week treatment is therefore recommended. Taken together with risks stated previously and the lack of available medical therapy for CHC in patients with decompensated cirrhosis, the risk benefit assessment is favorable for the regimen of LDV/SOF plus RBV administered for 12 weeks.

Limited subjects were enrolled in the posttransplant CPT C group to allow an adequate assessment of response. For posttransplant CPT C, the same 12 weeks of LDV/SOF plus RBV treatment duration is recommended. The basis for this recommendation is the observation of comparable virologic outcome in pre-transplant CPT B and CPT C groups despite differences in the degree of hepatic impairment. Specifically, similar SVR12 response 87% and 88% was observed in the pre-transplant CPT B and C groups, respectively; with few virologic relapsers (n=6 in CPT B, n=2 in CPT C). No striking differences in the safety profile were observed between pre-transplant CPT B and C groups, with RBV-induced anemia identified as the main toxicity. Therefore, the 12 week regimen is recommended in posttransplant CPT B patients is considered appropriate for posttransplant CPT C patients also.

Posttransplant subjects without cirrhosis and compensated cirrhosis – genotype 1 and 4
In posttransplant genotype 1 patients without cirrhosis or compensated cirrhosis (fibrosis F0-F3 or CPT A), the SVR12 response was 95% and 98% with 12 weeks and 24 weeks LDV/SOF plus RBV, respectively. Virologic relapse occurred in only three subjects; all three relapsers were in the 12 week treatment arm. For all genotype 1 relapsers, subgroup analysis did not identify consistent trends in any subgroup to justify the longer 24 week treatment compared to 12 weeks of treatment; and the 12 week treatment is therefore recommended for posttransplant patients without cirrhosis or with compensated cirrhosis.

For posttransplant genotype 4 patients without cirrhosis or compensated cirrhosis, the SVR12 response was 92% and 100% with 12 and 24 weeks treatment, respectively. Importantly, there were no virologic relapsers with the 12 weeks treatment. The risk-benefit assessment is favorable for LDV/SOF plus RBV for 12 weeks.

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1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for Postmarket Risk Evaluation and Mitigation Strategies related to the current sNDA S-007-009.

1.4 Recommendations for Postmarket Requirements and Commitments

The Division has determined that data from the Applicant's ongoing (b) (4) be submitted. Accordingly, the following postmarketing commitment (PMC) is recommended:

Collect, analyze and submit data on subjects with cirrhosis including decompensated cirrhosis who achieve sustained virologic response following treatment with a sofosbuvir-based regimen to evaluate durability of virologic response and to characterize clinical outcomes such as progression or regression of liver disease, liver-related mortality, occurrence of hepatocellular carcinoma, or liver failure requiring liver transplantation. Data collected should include 5 years of follow-up.

Final Protocol Submission:	08/18/2015
Study Completion:	10/20/2021
Final Report Submission:	10/20/2022

No new postmarketing requirements (PMR) are recommended in relation to the Pediatric Requirements Equity Act (PREA) because PREA PMRs to obtain data in pediatric age groups were issued previously for LDV/SOF.

2 Introduction and Regulatory Background

2.1 Product Information

Ledipasvir/sofosbuvir, marketed as Harvoni, is a fixed dose combination consisting of 90 mg ledipasvir plus 400 mg sofosbuvir. The fixed dose combination was originally approved in 2014 for the treatment of CHC genotype 1 infection in adults without cirrhosis or with compensated cirrhosis. In 2015, the indication was extended to adults with compensated cirrhosis with genotype 4, 5, or 6; and those with HIV-1/HCV genotype 1 or 4 coinfection.

The current applications propose expanding the indication to two new populations: 1) adult patients with decompensated liver disease (genotype 1); and 2) post-liver transplant recipients without cirrhosis or with compensated cirrhosis (genotype 1, 4).

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Both LDV and SOF are direct acting hepatitis C virus (HCV) antiviral agents. Sofosbuvir alone, marketed as Sovaldi, is also approved for the treatment of CHC in adults.

Table 1: Summary of product information

Generic name	ledipasvir/sofosbuvir FDC
Trade name	Harvoni
Pharmacologic classes	HCV NS5A inhibitor (LDV), HCV NS5B polymerase inhibitor (SOF)
Proposed indication	Treatment of CHC infection in patients with 1) Decompensated liver disease, irrespective of transplantation status 2) Post-liver transplant recipients
Dosage form	Oral tablet 90 mg LDV plus 400 mg SOF
Dose and regimen	One tablet taken once daily for 12 weeks
Age group	Adults

2.2 Tables of Currently Available Treatments for Proposed Indications

At the present time, no agents are approved for treating CHC in patients with decompensated liver disease. For post-liver transplant patients, only Viekira Pak is approved for use in patients with genotype 1 infection with fibrosis stage 0-2.

Table 2: Currently available treatments for proposed populations

Proposed Population	HCV Genotype	Available treatment
Decompensated liver disease	1-6	None
Post-liver transplantation with cirrhosis: compensated or decompensated	1-6	None
Post-liver transplantation with mild fibrosis (Metavir 0-2) and normal hepatic function	1	Viekira Pak

Viekira Pak, a DAA, is a combination regimen consisting of four agents, ombitasvir, paritaprevir, ritonavir, and dasabuvir. Of these, ombitasvir is an NS5A inhibitor, paritaprevir is an NS3/4 protease inhibitor, dasabuvir is an NS5B inhibitor, and ritonavir serves as a pharmacoenhancer.

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2.3 Availability of Proposed Active Ingredient in the United States

The LDV/SOF FDC is currently approved and marketed in the United States (U.S.).

2.4 Important Safety Issues With Consideration to Related Drugs

Currently approved NS5A inhibitors are LDV (a component of Harvoni), ombitasvir (a component of Viekira Pak and Technivie), and daclatasvir (DCV). Hepatic decompensation is the primary concern reported with Viekira Pak and Technivie. Use of Viekira Pak and Technivie is contraindicated in patients with decompensated cirrhosis, and product labeling includes Warnings and Precautions for hepatic decompensation and hepatic failure in cirrhosis. With DCV plus SOF, commonly reported side-effects include headache, fatigue, diarrhea, and nausea.

Sofosbuvir is the only approved NS5B nucleotide polymerase inhibitor. Serious symptomatic bradycardia is a concern with SOF and LDV/SOF. The concern is conveyed in product labeling as Warnings and Precautions, with continued ongoing postmarketing reviews by FDA CDER Office of Surveillance and Epidemiology (OSE) for additional safety concerns.

Important safety issues with RBV are presented here because the proposed regimen is LDV/SOF co-administered with RBV. Prior to the availability of HCV DAA therapies, RBV with interferon therapy was approved for the treatment of CHC and the safety profile of RBV is well-established. Hemolytic anemia is a prominent safety concern. Severe hemolytic anemia has been reported resulting in cardiac complications such as fatal as well as nonfatal myocardial infarction. Ribavirin is teratogenic, exerts embryocidal activity, and is classified as Pregnancy Category X. Use is contraindicated in women who are pregnant and in male partners of women who are pregnant, with additional caution to avoid pregnancy for six months after completion of RBV therapy. Rash and pruritus are frequently reported with RBV use.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Prior to submission of sNDA 007-009, the Division recommended the Applicant submit a proposal for the evaluation of drug-induced liver injury (DILI) in the SOLAR-1 and SOLAR-2 trial populations with decompensated cirrhosis and post-liver transplantation. Identification of DILI is challenging in these patients as traditional laboratory criteria used for screening can be difficult to interpret with advanced liver disease, multiple comorbidities, and use of multiple medications including immunosuppressive therapies. Discussions related to the topic are summarized here; other presubmission activities viewed as routine for incoming efficacy supplements are not presented.

Criteria for the identification of DILI

The Applicant's proposed DILI screening criteria and plan for DILI assessment submitted in the pre-sNDA meeting background package were considered reasonable by the Division; however, the Division recommended the inclusion of additional criteria at the pre-NDA face-to-face meeting.

Briefly, the originally proposed DILI screening criteria were based on opinions from experts in the field of hepatology and liver transplantation. The Applicant presented rationale for the utility of relative versus absolute cutoffs for ALT, AST, total and direct bilirubin; the value of increases from baseline versus the ULN for these individual parameters; and the accuracy of increases in parameter from the subject's nadir versus baseline:

- The Applicant proposed increase in direct bilirubin > 1 mg/dl from baseline as an appropriate criterion for screening DILI. In the SOLAR-1 and SOLAR-2 trials, criteria based on ALT or AST (for example, ALT > 5 x nadir) did not identify further cases beyond those identified by the proposed direct bilirubin cutoff; and ALT or AST based criteria were not proposed by the Applicant.

- Review of cases identified as possible DILI based on the proposed screening criteria will be performed by an independent adjudication committee composed of four experts, (b) (4)

The Division generally agreed with the Applicant's selection of direct bilirubin as a critical parameter of interest and the proposed adjudication process. In addition, the Division recommended the inclusion of the following two criteria to allow for thorough screening: subjects with increase in ALT or AST > 2 x baseline, and subjects with increase in ALT > 3 x postbaseline nadir.

The Division also recommended the independent adjudication committee review all treatment-emergent deaths, treatment-emergent liver transplantations, treatment-emergent SAEs of hepatic failure, hepatic AEs, and discontinuations due to pre-specified laboratory stopping criteria in order to capture all potential events of DILI. The Applicant agreed with the Division's recommendations. The final agreed-upon criteria to screen for potential DILI cases are shown below.

- Increase from baseline in direct bilirubin by 1 mg/dL
- AST or ALT > 2 x baseline value
- AST or ALT > 3 x post-baseline nadir value
- Discontinuation for protocol-specified laboratory stopping criteria: ALT and/or AST > 10 x baseline or nadir, or ALT > 15 x ULN
- Hepatic failure SAE

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- Treatment-emergent fatalities
- Treatment-emergent liver transplantation

Please refer to the pre-sNDA meeting minutes dated June 1, 2015 under IND 115268 in DARRTS for details.

2.6 Other Relevant Background Information

Context of baseline host and disease characteristics in the intended populations

Globally, 170 million people are estimated to be infected with HCV, which induces liver necrosis and inflammation and increases the risk of progressive liver failure and liver cancer. Patients with CHC infection who progress to advanced liver disease with hepatic decompensation (Child Pugh stage B or C) are at risk of life-threatening complications including hepatic encephalopathy, ascites, hepatorenal syndrome, and gastrointestinal variceal bleeding. Patients experience complications of portal hypertension such as recurrent variceal bleeding and recurrent ascites which result in hospitalizations. Shifts in fluid balance are present with ascites, transudative pleural effusion, pedal edema, and some patients develop hepatorenal syndromes. Such patients are also at increased risk of infections, in particular, spontaneous bacterial peritonitis. Without liver transplant, the one-year mortality for patients with Child Pugh stage C liver disease exceeds 50%, and for patients with Child Pugh stage B is estimated to be approximately 20%.

Patients who are posttransplant are on concomitant immunosuppressive agents to prevent rejection of the engrafted liver. These patients are at risk of infections including opportunistic infections e.g. progressive multifocal leukoencephalopathy (PML) due to immunosuppressive therapy.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Clinical site inspections conducted by CDER's Office of Scientific Investigations (OSI) did not raise concerns related to data integrity from the inspected sites. Four clinical sites with high enrollment were selected for inspection. The inspected sites included two U.S. and two foreign sites from the SOLAR-1 and SOLAR-2 trials, respectively. The OSI inspections concluded data from the four sites were acceptable. Please refer to the OSI inspection report for details.

3.2 Compliance with Good Clinical Practices

The Applicant certified the clinical trials supporting the sNDAs 007-009 were conducted in accordance with the ICH Good Clinical Practice (GCP) guidelines. Note that one trial, SOLAR-2, was conducted outside the U.S. and not under an IND; the Applicant has certified the conduct of SOLAR-2 trial was according to FDA requirements for IND studies. The Applicant also stated the trial protocols and amendments were reviewed and approved by independent ethics committees and Institutional Review Boards. Written informed consent was obtained from all subjects prior to trial-related procedures. The CDER OSI inspections of four clinical sites did not reveal evidence of GCP noncompliance. Please refer to section 3.1 and the OSI inspection report for details.

3.3 Financial Disclosures

Financial disclosure information as defined in 21 CFR 54.2(a), (b), or (c), was submitted for all investigators in the two trials supporting sNDAs 007-009. In one of the two trials, SOLAR-1, multiple investigators had significant financial arrangements with the Applicant. The implications of this finding, chiefly, the potential for investigator bias for key study endpoints were carefully considered by the review team. The statistical and clinical reviewers performed additional analyses to assess an impact on key endpoints. Based on the findings in additional analyses, the review team concluded a low likelihood of substantial investigator bias as a result of financial arrangements. Detailed considerations are presented below with additional information in Appendix 9.4 and Dr. Wen Zeng's statistical review.

Regarding the primary study endpoints, we acknowledge the primary efficacy endpoint, SVR 12, is not subject to investigator bias because this relies on an objective laboratory-based parameter HCV RNA measured by an independent entity ((b) (4)). Similarly, safety-related laboratory results are objective and not expected to be subject to investigator bias.

However, the review team was concerned about potential investigator bias in the causality assessment of important adverse events. We noted that all treatment-emergent deaths and treatment-emergent liver transplantations had been reviewed and assessed individually by an independent adjudication committee consisting of experts from the field of hepatology and liver transplantation. The same committee also adjudicated all hepatic serious adverse events and cases of potential DILI. For overall drug-related adverse events, we performed analyses excluding data from the implicated investigator sites in order to identify new or outstanding safety concerns. As part of the due diligence process, we also performed sensitivity analysis for the primary endpoint SVR 12 excluding data from the implicated sites. The findings from these additional

analyses did not raise major concerns; therefore, the review team concluded a low likelihood of substantial investigator bias due to financial interests.

In addition, OSI inspection of one investigator with significant financial interests did not reveal concern with data integrity at the clinical site. Please refer to section 3.1 and the OSI inspection report for details.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see the original NDA for descriptions related to chemistry, manufacturing and controls issues with drug product. No additional CMC data were submitted with the sNDA.

4.2 Clinical Microbiology

Virology analysis for the sNDAs 007-009 evaluated the prevalence of pre-treatment NS5A RAPs in the pooled SOLAR-1 and SOLAR-2 trials, the effect of NS5A baseline RAPs on treatment response, and treatment-emergent substitutions. Please refer to the virology review by Dr. Lisa Naeger for details; the main findings from her virology analysis are presented below.

<u>Virologic failures and relapsers</u>
A total of 27 virologic failures, defined as those not below the LLOQ at the time of treatment discontinuation or relapsers at post-treatment Week 12, were observed. Of the 27 virologic failures, 4 subjects were on-treatment failures who had discontinued treatment for an AE with HCV RNA > LLOQ at the time; and the remaining 23 subjects were relapsers. Fewer virologic failures were observed in CPT A/F0-F3 groups compared to CPT B or C groups [CPT C (12/27, 44%), followed by CPT B (11/27, 41%), and CPT A/F0-F3 (4/27, 15%) at baseline].

<u>Effect of baseline NS5A RAPs on response</u>
For genotype 1, the presence or absence of baseline NS5A RAPs did not impact response rates in the 12 week or 24 week treatment groups. The analysis for genotype 1 virologic relapsers is presented in Table 11 in section 6.1.7. There were very limited genotype 4 relapsers to identify compelling trends or form conclusions regarding the impact of baseline NS5A RAPs on response.

<u>Treatment-emergent substitutions</u>

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Treatment-emergent NS5A substitutions were observed in 78% (21/27) of virologic failures. The most frequent substitutions were at positions 93 (41%), 30 (33%), E237G (15%), 58 (11%), 31 (11%); and less than 10% of subjects had emergent substitutions at positions 28 and 24. For relapsers only, treatment-emergent substitutions were observed in 91% (21/23).

4.3 Preclinical Pharmacology/Toxicology

Please see the original NDA for preclinical pharmacology/toxicology findings. No new pharmacology/toxicology data were submitted in sNDAs 007-009. Updates made to label sections 8.1 and 8.2, Pregnancy and Lactation, are consistent with the format according to the Pregnancy and Lactation Labeling Final Rule.

4.4 Clinical Pharmacology

Brief summaries of new or relevant clinical pharmacology findings are provided in this section. Please see the clinical pharmacology/pharmacometrics review by Dr. Jeffry Florian for additional details.

4.4.1 Mechanism of Action

Ledipasvir and SOF are DAA agents against the hepatitis C virus. Ledipasvir is an inhibitor of the HCV NS5A protein which is required for viral replication. Sofosbuvir is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase which is required for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active triphosphate GS-461203.

4.4.2 Pharmacodynamics

Please refer to section 4.4.3.

4.4.3 Pharmacokinetics

This section focuses on pertinent pharmacokinetic (PK) information for LDV and SOF in hepatic impairment studies, and findings from a population PK analysis for the SOLAR-1 and 2 trials.

- In the hepatic impairment study, LDV plasma exposure was similar in subjects with severe hepatic impairment and control subjects with normal hepatic function. Population pharmacokinetics analysis in HCV-infected subjects indicate cirrhosis including decompensated cirrhosis have no clinically relevant effect on the exposure of LDV.

- For SOF, relative to subjects with normal hepatic function, the $SOF_{AUC0-24}$ were 126% and 143% higher in moderate and severe hepatic impairment, while the SOF metabolite GS-331007 AUC0-24 were 18% and 9% higher, respectively. Population pharmacokinetics analysis in HCV-infected subjects indicates cirrhosis including decompensated cirrhosis have no clinically relevant effect on the exposures of sofosbuvir and GS-331007.
- Population PK analysis from SOLAR-1 and 2 trial data verified the findings stated in the previous bullets.

5 Sources of Clinical Data

The chief sources of data are two phase 2 trials conducted in the proposed populations, namely CHC patients with decompensated liver disease and post-liver transplant patients.

The phase 2 trials are GS-US-337-0123 and GS-US-337-0124, referred to as SOLAR-1 and SOLAR-2, respectively, in this clinical review.

The two trials are identical in design and of similar size, the main difference being the geographic location of clinical sites. A total of 337 and 334 subjects were enrolled in SOLAR-1 and SOLAR-2, respectively. SOLAR-1 was conducted only at U.S. sites, and SOLAR-2 was conducted entirely outside the U.S. with sites in the European Union, Canada, Australia and New Zealand. Key features are displayed in section 5.1 and details provided in section 5.2.

5.1 Tables of Studies/Clinical Trials

Table 3: Overview of trial design, SOLAR-1 and 2

Trial	Population	Design and treatment regimen	Total # subjects enrolled; # randomized to 12 weeks/ 24 weeks treatment	Location of trial sites
GS-US-337-0123 (SOLAR-1)	Adults with CHC GT 1 or 4, treatment-naïve or treatment-experienced, with: 1) Decompensated liver disease regardless of the transplantation status, 2) Post-liver transplant with compensated or decompensated liver disease	Randomized, open-label, multicenter trials <u>7 groups</u> 1: Pre-transplant CPT B 2: Pre-transplant CPT C 3: Post-transplant fibrosis 4: Post-transplant CPT A 5: Post-transplant CPT B 6: Post-transplant CPT C 7: Post-transplant FCH 1:1 randomization in each group to 12 or 24 weeks treatment with LDV/SOF + RBV	n=337 1: 30/29 2: 23/26 3: 55/56 4: 26/25 5: 26/26 6: 5/4 7: 4/2	U.S.
GS-US-337-0124 (SOLAR-2)	Adults with CHC GT 1 or 4, treatment-naïve or treatment-experienced, with: 1) Decompensated liver disease regardless of the transplantation status, 2) Post-liver transplant with compensated or decompensated liver disease	Randomized, open-label, multicenter trials <u>7 groups</u> 1: Pre-transplant CPT B 2: Pre-transplant CPT C 3: Post-transplant fibrosis 4: Post-transplant CPT A 5: Post-transplant CPT B 6: Post-transplant CPT C 7: Post-transplant FCH 1:1 randomization in each group to 12 or 24 weeks treatment with LDV/SOF + RBV	n=333 1: 28/28 2: 25/26 3: 52/49 4: 34/33 5: 22/23 6: 3/5 7: 3/2	Europe, Canada, Australia New Zealand

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5.2 Review Strategy

In this review, the chief focus was analysis of outcomes for 12 weeks LDV/SOF + RBV versus 24 weeks LDV/SOF + RBV to determine the optimal treatment duration for each new population.

Data from the two trials, SOLAR-1 and 2, were pooled for analysis of efficacy and safety, because the trials had identical design and enrolled the same patient populations. The pooled dataset by trial groups is shown in Table 4.

Table 4: Groups by liver disease stage and transplant status

Group	CPT stage/ transplant status	LDV/SOF + RBV 12 weeks N=336	LDV/SOF + RBV 24 weeks N=334
1	Pre-transplant CPT B	58	57
2	Pre-transplant CPT C	48	52
3	Posttransplant F0-F3	107	105
4	Posttransplant CPT A	60	58
5	Posttransplant CPT B	48	49
6	Posttransplant CPT C	8	9
7	Fibrosing cholestatic hepatitis (FCH)	7	4

Source: ADSL dataset SOLAR -1 and 2 ISS, ISE

As the risk benefit decision-making process took into consideration the stage of liver disease (compensated cirrhosis versus decompensated cirrhosis), HCV genotype 1 or 4, and liver transplantation status, the following key analysis groups were identified and defined as shown in Table 5.

- Efficacy analysis was performed separately for genotype 1 and genotype 4.
- For safety analyses, genotype 1 and 4 data were pooled for all ITT subjects.
- For each genotype, efficacy analyses were performed by compensated versus decompensated liver disease status.
- For each genotype, efficacy analyses were also performed for individual CPT class.

Table 5: Definition of analysis cohorts of interest

Cohort	Group #
Pre-transplant decompensated	Groups 1 + 2
Posttransplant decompensated	Groups 5 + 6
All Decompensated	Groups 1 + 2 + 5 + 6
All Compensated	Groups 3 + 4
By individual group	Each group 1 through 7 analyzed separately

Reference ID: 3878679

5.3 Discussion of Individual Studies/Clinical Trials

SOLAR-1 or GS-US-337-0123
A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Ledipasvir Fixed-Dose Combination + Ribavirin Administered in Subjects Infected with Chronic HCV who have Advanced Liver Disease or are Post-Liver Transplant

Objectives

- To explore the antiviral efficacy of combination therapy with LDV/SOF + RBV for 12 or 24 weeks in subjects with advanced liver disease (either pre-liver transplant or not currently wait-listed) and post-liver transplant HCV subjects as measured by SVR12 (SVR12 defined as HCV RNA < Lower Limit of Quantification [LLOQ] 12 weeks post-treatment)
- To evaluate the safety and tolerability of LDV/SOF + RBV administered for 12 or 24 weeks in each patient population.

Design

This is a multi-center, open-label study in genotype 1 and 4 HCV-infected adult male and female subjects. Approximately 400 subjects were enrolled in the following 7 groups. As shown previously in Table 3, subjects were randomized 1:1 to 12 weeks or 24 weeks of treatment with LDV/SOF (given once daily) with RBV (given as a divided dose twice daily).

Cohort A – Decompensated patients

- Group 1: Subjects with cirrhosis and moderate hepatic impairment (Child-Pugh Class B; 7-9)
- Group 2: Subjects with cirrhosis and severe hepatic impairment (Child-Pugh Class C; 10-12); subjects with CPT scores >12 were excluded.

Cohort B – Post-liver transplantation

- Group 3: Subjects without cirrhosis (Metavir fibrosis stage F0-F3) and with no evidence of hepatic decompensation
- Group 4: Subjects with cirrhosis and mild hepatic impairment (Child-Pugh Class A; 5-6)
- Group 5: Subjects with cirrhosis and moderate hepatic impairment (Child-Pugh Class B; 7-9)
- Group 6: Subjects with cirrhosis and severe hepatic impairment (Child-Pugh Class C; 10-12); subjects with CPT scores >12 were excluded.
- Group 7: Subjects with aggressive recurrent disease after transplant with evidence of cholestasis (FCH or fibrosing cholestatic hepatitis)

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Main inclusion criteria
Chronic genotype 1 and 4 HCV-infected adult male and non-pregnant/non-lactating female subjects, ages 18 years or older, with advanced liver disease or who are post-liver transplant

Key procedures and monitoring
Study visits occurred at Day 1 and at the end of weeks 1, 2, 4, 6, 8, and 12 for subjects randomized to receive 12 weeks of study treatment. Study visits occurred at Day 1 and at the end of weeks 1, 2, 4, 6, 8, 12, 16, 20 and 24 for subjects randomized to receive 24 weeks of study treatment. On-treatment assessments included adverse events (AEs), MELD and CPT scores, vital signs, weight, physical exam, ECG (at Day 1 and weeks 4, 12, and 24), safety laboratory tests, HCV RNA, PK, study drug dosing adherence, urine pregnancy tests (females of childbearing potential only), and pregnancy prevention counseling.

Study endpoints
The primary efficacy endpoint is SVR12 (HCV RNA < l lower limit of quantitation [LLOQ] 12 weeks after last dose of study drug) for subjects. Secondary efficacy endpoints include:

- Proportion of subjects who attain SVR at 2, 4, 8 and 24 weeks after discontinuation of study drug (SVR2, SVR4, SVR8 and SVR24);
- Proportion of subjects who have HCV RNA < LLOQ by visit while on study treatment; absolute and change from Day 1 in HCV RNA through Week 8; virologic failure; and
- Change from Day 1 in MELD and CPT scores.

The primary safety endpoint is the proportion of subjects who discontinued from study drug for an AE.

<u>SOLAR-2 or GS-US-337-0124</u>
The design elements, objectives, study endpoints, and inclusion/exclusion criteria are identical to those for study SOLAR-1 (see Table 3). SOLAR-2 was conducted at sites outside the US and not conducted under IND.

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6 Review of Efficacy

Efficacy Summary

Efficacy data from two phase 2 trials, SOLAR-1 and 2, were reviewed in support of use of LDV/SOF in combination with RBV for the treatment of CHC in patients with decompensated liver disease or post-liver transplant patients. The primary efficacy endpoint was the proportion of subjects achieving SVR12, an accepted endpoint for CHC treatment representing virologic cure.

Genotype 1

In each of the seven treatment groups, the proportion of subjects achieving SVR 12 was generally similar or identical with 12 weeks or 24 weeks of LDV/SOF + RBV treatment, with the exception of Group 6 posttransplant CPT C which was of inadequate size to allow an assessment of response and was assessed separately. In groups 1-5 and 7, the SVR12 response rate ranged from 87% to 100% with 12 weeks of treatment.

In genotype 1 subjects, 25 and 19 subjects did not achieve SVR12 in the 12 and 24 week treatment arms, respectively. The primary reasons for not achieving SVR12 or non-response were death (n=22) or virologic relapse (n=20). Virologic relapse was observed in 14 (4%) and 6 (2%) subjects in the 12 week and 24 week treatment arms, respectively.

Because the majority of subjects receiving 12 weeks of treatment achieved SVR12 in groups 1-5, subgroup analysis focused on identifying those groups which may derive benefit from the longer 24 week treatment course. In subgroup analysis by demographic and baseline disease characteristics, no particular subgroup was shown to derive greater benefit with 24 weeks treatment compared to 12 weeks treatment. Likewise, in analysis by baseline NS5A RAPs, a convincing trend was not observed between groups with baseline NS5A RAPs compared to groups without baseline NS5A RAPs to indicate the need for 24 week treatment or the need for screening for NS5A RAPs prior to treatment. In light of anemia-related RBV discontinuations observed, an impact of RBV discontinuation on virologic relapse was explored. An effect of RBV discontinuation or duration of use on relapse rates was not observed. In summary, subgroup analyses did not identify a particular subgroup which may derive greater benefit with 24 weeks of treatment. In conclusion, data support the recommendation of 12 weeks of LDV/SOF + RBV for genotype 1 patients with decompensated cirrhosis CPT B or C, and for posttransplant patients CPT B.

In the posttransplant CPT C group, limited subjects were enrolled to allow for an adequate assessment of response with 7 and 9 subjects in the 12 week and 24 week treatment arms, respectively. The dosing recommendation for posttransplant CPT C patients relies on 1) similar SVR12 responses observed in the pre-transplant CPT B

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(87% with 12 weeks treatment) and C groups (88% with 12 weeks treatment) indicating similar outcome despite differences in the degree of hepatic impairment, and 2) the responses observed in posttransplant CPT B group. In posttransplant CPT B group, SVR12 response was observed in 89% of subjects treated for 12 weeks treatment, and provides support for the same treatment duration for posttransplant CPT C patients. Of note, subjects with CPT scores > 12 were excluded from trials; and this information will be conveyed in the label.

Genotype 4
In posttransplant compensated groups (F0-F3, and CPT A), SVR12 rates were 75% and 100% with 12 week and 24 week treatment, respectively, and no virologic relapsers were observed in either treatment arm. An added advantage of extending to 24 weeks treatment was not evident, and therefore it is reasonable to conclude the 12 week LDV/SOF + RBV treatment is an appropriate duration for genotype 4 patients with posttransplant compensated liver disease.

Limited subjects were enrolled in the genotype 4 decompensated groups to allow an adequate assessment of efficacy to recommend a dosing regimen.

6.1 Indication

In the current sNDAs S-007 to 009, the Applicant has proposed to expand the existing indication, namely, for use in the treatment of CHC infection, to new populations with 1) decompensated cirrhosis, or 2) post-liver transplant patients. The efficacy of LDV/SOF, with or without RBV, was previously established in genotype 1 and 4 CHC patients with compensated cirrhosis or without cirrhosis.

6.1.1 Methods

Data sources and efficacy endpoints
The efficacy data from two pivotal trials, SOLAR-1 and 2, were reviewed in support of the use of LDV/SOF with RBV for the treatment of CHC in patients with decompensated liver disease or patients who are post-liver transplantation.

The primary efficacy endpoint was the proportion of subjects achieving SVR12, an accepted endpoint for CHC treatment. Specifically, SVR12 was defined as HCV RNA below LLOQ at post-treatment Week 12. In both trials, HCV RNA was measured by COBAS AmpliPrep/COBAS TaqMan HCV Test v2.0 with a lower limit of quantification of 15 IU/mL.

Additional proposed efficacy-related outcomes were reviewed including change from baseline in CPT scores at the post-treatment Week 12 and Week 24 timepoints, and

change from the baseline MELD score at post-treatment Week 12 and Week 24 timepoints. Change from baseline in CPT and MELD scores were pre-specified secondary efficacy endpoints in each pivotal trial, however the totality of the data for this endpoint are limited, and the clinical value of this exploratory endpoint is not well understood at present. A PMC will be requested to submit longer term data to support these endpoints and their impact on clinical endpoints including mortality.

Strategy for review of efficacy data

As stated previously, the efficacy of LDV/SOF treatment was established previously in less advanced populations with compensated cirrhosis or no cirrhosis. The SOLAR trials were designed to evaluate the optimal duration of LDV/SOF + RBV treatment – 12 weeks versus 24 weeks – in patients with decompensated cirrhosis or post-liver transplantation. Including a placebo arm as control in the trials was unethical and including an active control was not feasible because no agents were approved for use in the trial populations at the time the trials were conducted.

The two pivotal trials, SOLAR-1 and 2, were identical in design which enabled the pooling of data. Separate efficacy analyses were performed for groups with genotype 1 or genotype 4 infection.

Within genotype, the analyses focused on characterizing efficacy with 12 weeks vs. 24 weeks in the major groups shown below. Within each decompensated cohort, efficacy was analyzed separately for CPT B or C groups. Finally, efficacy was analyzed separately for the posttransplant CPT A and F0-F3 groups.

- Pre-transplant decompensated cirrhosis [CPT B + C]
- Posttransplant compensated cirrhosis or no cirrhosis [CPT A + F0-F3]
- Posttransplant decompensated cirrhosis [CPT B + C]

The Applicant and the FDA statistical analyses are based on individual subject's CPT stage on treatment Day 1 and not the stage observed at randomization. Shifts in the CPT score between the randomization day and treatment Day 1 visit resulted in re-assignment of some subjects to a different CPT group. Such re-assignment due to fluctuations in hepatic clinical (ascites, encephalopathy) and laboratory (bilirubin, albumin, INR) parameters between the date of randomization and study day 1 or baseline is not unexpected. Importantly, the randomization to either 12 or 24 weeks of treatment was maintained in all subjects. Please refer to the Dr. Wen Zeng's statistical review for details.

Efficacy analysis excluded subjects who were transplanted before posttreatment Week 12 and with the last available HCV RNA below LLOQ. Review of individual liver transplant cases occurring within 30 days of treatment discontinuation indicates the transplants were performed because of organ availability in previously enlisted patients or for exceptional circumstances (refer to section 7.3 for details); therefore, it is appropriate to censor the cases.

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Please note the separate efficacy analyses for the individual SOLAR-1 and SOLAR-2 trials were performed by Dr. Zeng. Dr. Zeng concluded the primary efficacy analysis findings were similar in the two pivotal trials. Only results from the pooled analysis are presented in this clinical review. The reader is referred to Dr. Zeng's statistical review for analysis by individual trial, as well as detailed subgroup and sensitivity analyses.

6.1.2 Demographics

The intent-to-treat population (ITT) included 670 subjects, 336 of whom received 12 weeks treatment and 334 received 24 weeks of treatment (Table 6). Of the 670 subjects, 215 and 455 subjects were pre-transplant and post-liver transplant, respectively. A total of 329 subjects with decompensated cirrhosis were enrolled; this includes 78 subjects with baseline MELD scores greater than 15.

Table 6: Baseline disease characteristics of the trial populations

Group	CPT stage/ transplant status	LDV/SOF + RBV 12 weeks N=336	LDV/SOF + RBV 24 weeks N=334
1	Pre-transplant CPT B	58	57
2	Pre-transplant CPT C	48	52
3	Posttransplant F0-F3	107	105
4	Posttransplant CPT A	60	58
5	Posttransplant CPT B	48	49
6	Posttransplant CPT C	8	9
7	Fibrosing cholestatic hepatitis (FCH)	7	4

Source: ADLS dataset SOLAR -1 and 2 pooled ISE

Group 3, posttransplant patients with F0-F3 fibrosis, enrolled 107 and 105 subjects in the 12 week and 24 week treatment arms, respectively. Groups 1, 2, 4, and 5 were similar in size with approximately 48-58 subjects in each treatment duration arm. In the posttransplant CPT C group 6, few subjects were enrolled with 8 or 9 subjects in each treatment duration arm. Few subjects were also enrolled in group 7 with FCH.

In the pooled dataset, 337 subjects were enrolled at sites in the U.S., 241 subjects were enrolled at sites in the European Union, and the remaining 92 subjects were enrolled at sites located in Canada, Australia, and New Zealand.

The majority of subjects, n=626, had genotype 1 infection; and 41 had genotype 4 infection. The trial demographics and baseline disease characteristics for genotype 1 are presented initially followed by genotype 4.

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Genotype 1
A total of 626 subjects with genotype 1 CHC infection were included in the pooled data. Baseline demographic characteristics including gender, race and age were comparable between the treatment durations for individual groups. The majority of subjects were male (77%) and Caucasian (92%). The majority of subjects were genotype 1a (72%) with fewer genotype 1b subjects (27%). The individual groups were generally balanced for 1a or 1b subtype with the exception of posttransplant CPT C group 6. In posttransplant CPT C group 6, 72% and 44% subjects, respectively, were genotype 1a in the 12 week and 24 week treatment arms; with the remaining subjects with genotype 1b. The majority of subjects were treatment-experienced (80%).

Compared to the pre-transplant groups, posttransplant groups had lower median GFR (66 mL/min) at baseline compared to pre-transplant groups (89 mL/min). Baseline median GFR was generally balanced between the treatment durations for each group. In decompensated groups, the majority of subjects had baseline MELD scores between 10 and 15. The baseline MELD scores were comparable between the treatment duration arms.

Genotype 4
A total of 41 subjects with genotype 4 CHC infection were included. The demographic and baseline disease characteristics were comparable between the treatment durations, and in general were similar to those described for genotype 1 patients above.

6.1.3 Subject Disposition

Overall, 673 subjects were randomized 1:1 to 12 weeks or 24 weeks treatment with LDV/SOF + RBV, respectively. Three randomized subjects did not receive treatment because the subject died prior to receiving any treatment (n=1), investigator's decision (n=1), and protocol violation (n=1). A total of 670 subjects received at least one dose of treatment including 336 and 334 subjects randomized to 12 and 24 weeks of treatment, respectively. Of the 670 ITT subjects, 215 and 455 subjects were pre-transplant and posttransplant, respectively. Of the 670 subjects, 628 subjects (94%) completed the trial and 42 subjects (6%) discontinued LDV/SOF treatment prematurely, as shown in Table 7. The common reasons for discontinuing treatment were due to an AE (n=19), death (n=8), liver transplantation (n=7), and investigator's discretion (n=3), as shown in the table below.

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Table 7: Disposition of trial participants, SOLAR-1 and SOLAR-2 pooled

Reason for disposition event	N=670 n (%)
Completed treatment	628 (94)
Discontinued treatment	42 (6)
Discontinued due to adverse event	19 (3)
Death	8 (1)
Liver transplantation	7 (1)
Investigator's discretion	3 (<1)
Noncompliance	2 (<1)
Lost to follow-up	1 (<1)
Protocol violation	1 (<1)
Withdrew consent	1 (<1)

Source: disposition analysis datasets SOLAR -1 and 2 ISS

In addition, three subjects who received treatment were excluded from the efficacy analysis because these pre-transplant subjects had CPT scores 5 or 6 (CPT A stage) on treatment day 1, and did not meet the protocol defined requirement for decompensated cirrhosis.

6.1.4 Analysis of Primary Endpoint

Separate efficacy analysis was performed for genotype 1 and genotype 4 subjects. In addition to analysis for those attaining SVR12 (responders), analysis for nonresponders was performed to determine the drivers for nonresponse. In particular, the proportion of subjects who relapsed was analyzed for each genotype. Findings from these three analyses are presented below.

Genotype 1 - Primary Endpoint Analysis

1) *Responder Analysis for SVR12*

Table 8 below summarizes the primary efficacy outcome by group and treatment duration. The primary endpoint is the proportion of subjects achieving SVR12, defined as HCV RNA below LLOQ at post-treatment Week 12. Within each group, the proportion of subjects achieving SVR12 was similar or identical in the 12 week and 24 week treatment arms, with the exception of group 6 discussed separately in section 6.1.8.

Table 8: SVR12 response for genotype 1 CHC, SOLAR-1 and 2 pooled

Cohort	Group/ Stage	LDV/SOF + RBV 12 weeks	LDV/SOF + RBV 24 weeks
Pre-transplant decompensated	1: CPT B	86.5% (45/52)	92.0% (46/50)
	2: CPT C	87.5% (35/40)	82.6% (38/46)
Posttransplant	3: F0-F3 Fibrosis	95.0% (94/99)	99.0% (99/100)
	4: CPT A	98.2% (55/56)	96.2% (51/53)
	5: CPT B	89.1% (41/46)	95.6% (43/45)
	6: CPT C	57.1% (4/7)	77.8% (7/9)
	7: FCH	100% (7/7)	100% (4/4)

Source: statistical review NDA 205834 S007-009/GAM-2 statistical presentation; ADEFF ISE SOLAR-1 and 2

Groups 1-5

In each of the groups 1-5, treatment differences between 12 and 24 week treatment arms were no more than 6%. A consistent trend favoring the 24 week treatment duration was not identified as lower SVR12 rate with 24 weeks treatment compared to 12 weeks treatment was observed in groups 2 and 4.

Additionally, it should be noted groups 3 and 4 who are posttransplant without cirrhosis or with compensated cirrhosis had relatively higher SVR12 rates (95% to 99%), compared to SVR12 rates in groups 1, 2, or 5 with decompensated cirrhosis (83% to 96%). Patients with decompensated cirrhosis are distinct and more likely to develop complications of portal hypertension (e.g., gastric variceal bleeding) which may be fatal and potentially contribute to nonresponse. An additional analysis of nonresponders was performed to determine whether virologic failure or relapse was the primary driver for or if other factors such as death contributed to the differential response rates; this analysis is presented later in this section.

Group 6

As stated previously, group 6 enrolled a limited number of subjects to allow an adequate assessment of response. In this group, 57% and 78% of subjects in the 12 and 24 weeks treatment arms achieved SVR12. The findings in this group are outstanding with substantially lower SVR12 rates compared to the other groups, and the notable improvement in response with 24 weeks treatment. Three and two subjects in the 12 and 24 weeks treatment arms, respectively, did not achieve SVR12 indicating a small numerical difference in nonresponders. Further analysis was performed to explore the reasons for not achieving SVR12 in this group and is discussed later in this section. The dose recommendation considerations for posttransplant CPT C are presented in section 6.1.8.

Group 7

In posttransplant patients with FCH, all subjects achieved SVR12 (100%) regardless of the duration of treatment. While limited subjects were enrolled in group 7, the findings

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of 100% SVR12 rate are striking and indicate 12 weeks of LDV/SOF + RBV is the appropriate treatment duration. Although FCH is an aggressive form of cirrhosis, such patients may not necessarily have decompensated cirrhosis. In fact, the 11 FCH subjects in group 7 had compensated cirrhosis at baseline. The observed SVR12 response rate is therefore not unexpected in light of response rates in posttransplant groups 3 and 4 with compensated cirrhosis or without cirrhosis.

2) Nonresponder analysis

Overall, 25 and 19 subjects did not achieve SVR12 in the 12 and 24 week treatment arms, respectively. As shown in Table 9 below, few subjects did not achieve SVR12 within the individual groups 1-6. The primary reason for not achieving SVR12 was death (n=22) and virologic relapse (n=20). None of the treatment-emergent deaths were attributed to study treatment (refer to section 7.3.1). Virologic relapse, defined as subjects with HCV RNA suppressed at end of treatment and above LLOQ at post-treatment Week 12, was observed in 14 (4%) and 6 (2%) subjects, respectively, in the 12 and 24 week treatment arms.

Table 9: Nonresponder analysis for genotype 1 CHC, SOLAR-1 and 2 pooled

Cohort	Group/ stage	12 weeks LDV/SOF + RBV (N=336)			24 weeks LDV/SOF + RBV (N=334)		
		Non responder	Nonresponder due to relapse	Nonresponder for other reason*	Non responder	Nonresponder due to relapse	Nonresponder for other reason*
Pre-transplant	1: CPT B	7/52	6/52	1/52	4/50	2/50	2/50
	2: CPT C	5/40	2/40	3/40	8/46	3/46	5/46
Post transplant	3: F0-F3	4/99	3/99	1/99	1/100	0	1/100
	4: CPT A	1/56	0	1/56	2/53	0	2/53
	5: CPT B	5/46	1/46	4/46	2/45	0	2/45
	6: CPT C	3/7	2/7	1/7	2/9	1/9	1/9
	7: FCH	0/7	0	0	0/4	0	0

*Other reasons for not achieving SVR12 include death (n=22), withdrew consent (n=2).
Source: ADEFF dataset SOLAR-1 and 2 ISE

3) Virologic relapse analysis

Overall, virologic relapse was observed in 14 (4%) and 6 (2%) subjects, respectively, in the 12 and 24 week treatment arms, with 2% difference in relapse rates (refer to Table 9).

Groups 1 and 2: In pre-transplant subjects with CPT B, virologic relapse was observed in 6 versus 2 subjects, respectively, in the 12 and 24 weeks treatment arms. In contrast, in pre-transplant subjects with CPT C, virologic relapse was observed in 2

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versus 3 subjects, respectively, in the 12 and 24 weeks of treatment. In subjects with CPT B plus C (groups 1 plus 2), virologic relapse was observed in 7% (8/92) and 4% (5/96) of subjects, respectively, in the 12 and 24 week treatment arms.

Group 5: In the posttransplant subjects with CPT B, virologic relapse was observed in 1 versus zero subjects, respectively, in the 12 and 24 weeks of treatment.

Group 6: In posttransplant CPT C, virologic relapse was observed in 2 versus 1 subject, respectively, in the 12 and 24 week treatment arms.

Groups 3 and 4: In posttransplant subjects without cirrhosis or with compensated cirrhosis, virologic relapse was observed in only three subjects. The three subjects had received 12 weeks of LDV/SOF + RBV. No virologic relapse was observed in subjects receiving 24 weeks treatment.

To summarize, the majority of genotype 1 subjects in each group attained SVR12. Death (n=22) and virologic relapse (n=20) were the primary reasons for not achieving SVR12. The overall relapse rate was 4% and 2%, respectively, in the 12 and 24 week treatment arms. However, a trend of higher relapse rate with 12 week treatment was not consistently observed in each group; for example, group 1 and group 2. Differences in relapse between 12 and 24 weeks of treatment should be cautiously interpreted in light of the small number of relapse cases, lack of a consistent trend across the groups, and because the trials were not powered for such analyses.

Genotype 4 - Primary Endpoint Analysis

Group 3: In posttransplant F0-F3 stage subjects, SVR 12 response rate was 100% with both 12 weeks (8 out of 8 subjects) and 24 weeks (5 out of 5 subjects) treatment. Previously, LDV/SOF alone for 12 weeks treatment duration was approved for the treatment of genotype 4 CHC infection in pre-transplant patients with compensated cirrhosis. The findings in Group 3 are compelling and support 12 weeks of treatment with LDV/SOF + RBV based on 100% response observed, and taking into consideration the established 12-week regimen of LDV/SOF alone in pre-transplant compensated patients.

Group 4: In posttransplant CPT A subjects, the SVR12 response rate was 75% (3 out of 4 subjects) and 100% (5 out of 5 subjects), respectively, in the 12 and 24 week treatment arms. The subject who did not achieve SVR12 did not experience virologic relapse. It is reasonable to conclude the 12 week LDV/SOF + RBV treatment duration is supported for posttransplant CPT A patients based on findings in Group 4, and in light of compelling findings in Group 3, and taking into consideration the approved 12-week duration of LDV/SOF treatment in pre-transplant compensated cirrhosis as discussed in the previous bullet.

Table 10: SVR12 analysis for genotype 4 CHC, SOLAR-1 and 2 pooled

Cohort	Group/ stage	LDV/SOF + RBV 12 weeks	LDV/SOF + RBV 24 weeks
Pre-transplant (decompensated)	G1: CPT B	75% (3/4)	100% (2/2)
	G2: CPT C	33% (1/3)	50% (1/2)
Posttransplant	G3: F0-F3 Fibrosis	100% (8/8)	100% (5/5)
	G4: CPT A	75% (3/4)	100% (5/5)
	G5: CPT B	100% (2/2)	75% (3/4)
	G6: CPT C	0 (0/1)	0
	G7: FCH	0	0

Source: statistical review NDA 205834 S007-009;GAM-2 statistical presentation; ADEFF SOLAR-1 and 2 ISE

Genotype 4 decompensated cirrhosis, pre-transplant or posttransplant:
Note the Applicant is not seeking an indication or dose recommendation for genotype 4 decompensated cirrhosis, for either pre-transplant or posttransplant patients. For groups 1, 2, 5, and 6, the available data are from very few subjects in each subgroup. The data are insufficient to characterize efficacy in these population groups and no definite conclusions for duration of therapy can be derived from the submitted data.

6.1.5 Analysis of Secondary Endpoints

Changes in CPT and MELD score from baseline to post-treatment Week 12 and 24 were analyzed by Dr. Zeng. Analysis was performed for 123 subjects with decompensated cirrhosis who achieved SVR 12 and for whom data were available.

Change in CPT score
Of the subjects achieving SVR12 with 12 weeks treatment, 60% (74/123) and 34% (42/123) had an improvement or no change in CPT scores from baseline to post-treatment week 12, respectively. Of the 32 subjects who had CPT C cirrhosis at baseline, 53% (17/32) had CPT B cirrhosis at post-treatment Week 12. Of the 88 subjects who had CPT B cirrhosis at baseline, 25% (22/88) had CPT A cirrhosis at post-treatment Week 12. Improvement in CPT score was driven by improvement in albumin and bilirubin.

Change in MELD score
Of the subjects achieving SVR12 with 12 weeks treatment, 57% (70/123) and 19% (23/123) had an improvement or no change in MELD score from baseline to post-treatment week 12, respectively. Of the 32 subjects whose MELD score was ≥ 15 at baseline, 59% (19/32) had a MELD score < 15 at post-treatment Week 12. Improvement in MELD score was driven primarily by improvement in bilirubin.

Analysis of the above parameters was performed for the submitted post-treatment Week 24 data. The post-treatment Week 24 findings were generally similar to post-treatment week 12 findings presented above.

(b) (4)

Additional data will need to be reviewed, including data from a postmarketing study where data will be collected from a 5-year cirrhosis registry study. We are recommending a PMC is issued to the Applicant to submit longer term data to support these endpoints and their impact on important clinical endpoints.

6.1.6 Other Endpoints

Additional endpoint analyses were not performed by the clinical reviewer. Please refer to Dr. Wen Zeng's statistical review for sNDAs 007-009.

6.1.7 Subpopulations

The primary endpoint analyses demonstrate that the 12 weeks treatment duration is appropriate for the majority of subjects in individual groups. In subgroup analyses, the review team focused on identifying those subgroups which may benefit with the longer 24 weeks treatment.

Subgroup analysis was performed for genotype 1 only; no subgroup analysis was performed for genotype 4 because no virologic relapse occurred in the genotype 4 groups without cirrhosis or with compensated cirrhosis, and because the Applicant is not seeking an indication for the genotype 4 decompensated cirrhosis populations.

Subgroup analysis was performed for key factors known to influence outcomes with CHC treatment including gender, age, HCV genotype, baseline BMI, baseline HCV RNA and other important baseline characteristics. Analysis for these subgroups was performed by Dr. Zeng for SVR12 responders and virologic relapsers. The presence of baseline RAPs has been shown to affect the efficacy of some DAA regimens, and analysis by baseline NS5A RAPs was performed by virology reviewer, Dr. Lisa Naeger. In addition, the review team recognized higher rates of RBV discontinuation secondary to anemia, especially in the groups with decompensated cirrhosis. An analysis for duration of RBV use in relapsers was therefore performed by Dr. Jeff Florian.

Analysis by demographic and baseline disease characteristics, Genotype 1

- In subjects achieving SVR12, the response rates were comparable between the 12 weeks and 24 weeks treatment arms in the key subgroups. A trend of lower

SVR12 rates (≥ 5% difference) with 12 week treatment compared to 24 week treatment was observed in the following subgroups: males (84% versus 89%), genotype 1b (83% versus 91%), and IL28BCT (82% versus 92%).

- In virologic relapsers, a trend for higher relapse rate (≥ 5% difference) with 12 week treatment compared to 24 week treatment was observed in the following subgroups: baseline BMI ≥ 30 kg/m^2 (17% versus 8%), genotype 1b (10% versus 2%), IL28BCC (11% versus zero), baseline HCV RNA ≥ 800,000 IU/mL (10% versus 5%). It should be noted the findings were observed in subgroups of very limited size, and the observations should be interpreted with caution.

- Additional logistic regression analysis including multivariate analysis were performed by the Applicant and verified by Dr. Zeng. The only factor associated with higher relapse rate with 12 weeks treatment compared to 24 weeks of treatment was baseline BMI ≥ 30 kg/m^2. It should be noted the findings were observed in a subgroup of limited size, with only 11 relapsers with baseline BMI ≥ 30 kg/m^2. Of these, 8 subjects were in the 12 week treatment arm (8/48 or 17%) and 3 subjects were in the 24 week treatment arm (3/36 or 8%). Also, see Dr. Wen's statistical review for details.

The subgroup analysis findings for compensated post-liver transplant patients (groups 3, 4) were similar to those for decompensated patients with no new trends noted. All group 7 FCH subjects responded regardless of baseline characteristics.

Impact of baseline NS5A RAPs on relapse, Genotype 1

The impact of baseline NS5A RAPs on relapse rates was evaluated by the virology reviewer Dr. Lisa Naeger. Dr. Naeger performed analysis for genotype 1 subjects who relapsed (Table 11). Most of the relapsers were GT1a (n=14). Of the 20 relapsers, 5 relapsers had baseline NS5A RAPs, and the remaining 15 had no NS5A RAPs at baseline.

In subjects with baseline NS5A RAPs, the relapse rates were as follows:

- In genotype 1a CPT C groups, 33% (1/3) and zero subjects relapsed with 12 weeks and 24 weeks treatment, respectively
- In genotype 1a compensated posttransplant groups, 13% (3/23) and zero subjects relapsed with 12 weeks and 24 weeks treatment, respectively
- In genotype 1b CPT C groups, 20% (1/5) and zero subjects relapsed with 12 weeks and 24 weeks treatment, respectively

The finding of increased relapse rates for the aforementioned groups for the 12 week treatment duration is interpreted cautiously because the numbers of subjects in individual subgroups are small. Importantly, for the No NS5A RAPs subgroups, relapse rates were 9% and 18% for CPT C groups with 12 and 24 weeks treatment,

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respectively. The overall relapse rates in the No NS5A RAPs subgroups indicate factors other than baseline NS5A RAPs contributed to relapse. In conclusion, there are a limited number of subjects in individual subgroups and no convincing trend was identified to recommend 24 weeks treatment or to recommend screening at baseline for NS5A RAPs.

Table 11: Baseline NS5A resistance associated polymorphisms and virologic relapse, SOLAR-1 and 2

	w/NS5A RAPs		No NS5A RAPs	
GT1a	12 WK	24 WK	12 WK	24 WK
B (Grp 1 and 5)	0% (0/12)	0% (0/13)	6% (3/48)	2% (1/47)
C (Grp 2 and 6)	33% (1/3)	0% (0/5)	9% (2/23)	18% (4/24)
Compensated post TX (Groups 3 and 4)	13% (3/23)	0% (0/17)	0% (0/75)	0% (0/78)
GT1b				
B (Grp 1 and 5)	0% (0/9)	0% (0/10)	17% (4/24)	5% (1/20)
C (Grp 2 and 6)	20% (1/5)	0% (0/9)	0% (0/12)	0% (0/13)
Compensated post TX (Groups 3 and 4)	0% (0/19)	0% (0/18)	0% (0/34)	0% (0/35)

Source: Dr. Lisa Naeger's virology review NDA 205834 S007-009

Impact of the duration of RBV use on relapse

All 23 relapsers, including genotype 1 and 4 subjects, had completed LDV/SOF treatment for the assigned duration of 12 weeks or 24 weeks. Of the 23 relapsers, only 2 subjects had discontinued RBV prematurely and 21 subjects relapsed despite completing the assigned RBV treatment, as discussed below:

- One subject, posttransplant CPT C in the 12 week treatment arm, had discontinued RBV at the Week 8 visit and continued LDV/SOF for 12 weeks.
- Another subject, posttransplant CPT C in the 24 week treatment arm, had discontinued RBV at the Week 4 visit and continued LDV/SOF for 24 weeks.

The majority of relapsers had completed RBV treatment. Early discontinuation of RBV was observed in only two relapsers. The finding suggests that a shortened duration of RBV use is not the primary driver of virologic relapse in the SOLAR-1 and 2 trials. Additionally, relapse in one subject who discontinued RBV at Week 4 and completed 24 weeks of LDV/SOF suggests LDV/SOF alone for 24 weeks may not be an effective alternative in patients who are unable to tolerate RBV.

As discussed in section 4.4.2, the observed lack of impact of RBV on relapse is not unexpected. Analyses performed by Dr. Florian show the majority of subjects were able to tolerate RBV. The chief reason for discontinuing RBV treatment was anemia which

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persisted in spite of supportive therapies such as blood transfusions. In subjects who discontinued RBV early, the median time of RBV discontinuation was approximately 4-6 weeks.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dose recommendation considerations for Genotype 1 Posttransplant CPT C

In the posttransplant CPT C group 6, limited subjects were enrolled to allow for an adequate assessment of response with 7 and 9 subjects in the 12 week and 24 week treatment arms, respectively.

The dosing recommendation for genotype 1 patients with posttransplant CPT C relies on the following observations in SOLAR-1 and 2 trials:

1) Similar SVR12 responses observed in the pre-transplant CPT B (87% with 12 weeks treatment) and C groups (88% with 12 weeks treatment) indicating similar outcome despite differences in the degree of hepatic impairment, and
2) The response observed in posttransplant CPT B group: In posttransplant CPT B group, SVR12 response was observed in 89% of subjects treated for 12 weeks treatment, and provides support for the same treatment duration for posttransplant CPT C patients.
3) Based on above considerations, the 12 week treatment duration is reasonable for posttransplant CPT C patients.

The overall risk benefit assessment for posttransplant CPT C patients is discussed in section 1.2 of this review.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Efficacy data beyond post-treatment Week 12 were not available for all SOLAR-1 and SOLAR-2 subjects at the time of submission of the current supplements S-007 to S-009. The Applicant has stated plans to submit SVR24 data in the final clinical study report submitted for each trial. Of note, high rates of concordance between SVR24 and SVR12 have been demonstrated for previously approved CHC treatments. Specifically for LDV/SOF containing regimens, 100% concordance was observed between SVR12 and SVR24 in previously conducted ION-1 and ION-2 trials. In the field of CHC treatment, SVR is an accepted surrogate marker for virologic cure. Achieving SVR was shown to result in the histologic improvement of fibrosis, reduced progression of fibrosis, reduced mortality, and improved quality of life in CHC populations with less advanced disease.

6.1.10 Additional Efficacy Issues/Analyses

There are no additional efficacy issues.

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7 Review of Safety

Safety Summary

In the current sNDAs, the observed adverse event profile was consistent with the previously characterized safety profile for each product LDV/SOF or RBV, and reflected the underlying liver disease and associated comorbidities of the treated population.

- An unexpected trend in the known LDV/SOF and RBV toxicity profile, or a new toxicity concern was not identified with the 12 week dosing regimen. LDV/SOF was well-tolerated in the majority of subjects with few discontinuations overall in 3% of subjects.
- The safety profile LDV/SOF was comparable between the 12 week and 24 week treatment durations.
- Compared to posttransplant groups without cirrhosis or with compensated cirrhosis, the groups with decompensated cirrhosis subjects (1, 2, 5, 6) had proportionally more deaths, nonfatal SAEs, and treatment discontinuations than compensated liver disease groups. In each group with decompensated cirrhosis subjects, the AE was profile more pronounced in CPT C compared to CPT B groups. These findings are not unexpected as the presence and severity of underlying hepatic impairment may affect the likelihood of developing complications such as gastrointestinal variceal bleeding and other comorbidities including infections.

Deaths and liver transplants
Overall, treatment-emergent deaths were observed in 20 (3%) subjects. None of the deaths were attributed to study treatment by the investigators or the independent adjudication committee (IAC) consisting of four external hepatology experts. The majority of deaths (16/20) were in decompensated subjects. In four cases, death was attributed to natural progression of liver disease. We agree with the investigator assessment and IAC adjudication while acknowledging the challenges in discerning drug toxicity in highly complicated settings where progression of liver disease and resultant death are not unexpected.

Treatment-emergent liver transplants were performed in 11 (2%) subjects overall. None of the transplants were attributed to study treatment by the investigators or the IAC. All subjects had decompensated liver disease at baseline. Subjects were transplanted because an appropriately matched organ had become available, or because the MELD scores increased in the setting of infection or sepsis or secondary to complications of cirrhosis-related procedure.

Nonfatal SAEs, discontinuations, common AEs
Overall, nonfatal SAEs regardless of causality were reported in 127 (22%) subjects; while, treatment-related SAEs were reported in 19 (3%) subjects. The majority of SAEs

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were in decompensated cirrhosis groups, and were assessed unrelated to study treatment, and were secondary to the underlying advanced liver disease and consistent with the enrolled population. Among treatment-related SAEs, ribavirin-induced anemia events were most frequently observed. Excluding anemia, treatment-related SAEs were observed in seven subjects (1%).

A total of 20 (3%) of subjects discontinued LDV/SOF due to an AE. Again, the majority of discontinuations were in decompensated cirrhosis groups (15/20) and the remaining five discontinuations were in groups with compensated cirrhosis or without cirrhosis. The AEs resulting in treatment discontinuation in at least two subjects were gastric hemorrhage or gastric varices hemorrhage (n=2), sepsis (n=2), hepatocellular carcinoma (n=2), dyspnea (n=2), and acute renal failure (n=2).

The commonly occurring adverse drug-related events or ADRs in the trial population were similar to those previously reported with LDV/SOF and/or RBV use and are currently labeled for these agents. ADRs reported in at least 20% of subjects were fatigue, headache, nausea, anemia, and pruritus.

<u>DILI</u>
A concern for DILI was not identified in the SOLAR-1 and 2 trial population. All treatment emergent deaths and liver transplants were assessed as unlikely to be treatment-related by the IAC consisting of independent hepatology experts. Four possible cases of DILI were confounded by the underlying hepatic disease and/or concurrent use of potentially hepatotoxic medication, and not attributed to study treatment by the IAC. In 11 separate cases, mild increases in ALT or AST from baseline or nadir were observed, without an associated rise in direct bilirubin. These ALT or AST increases were in posttransplant patients with compensated cirrhosis or without cirrhosis; the observed increases were transient, resolved without intervention, and were assessed by the IAC to be of trivial clinical significance. While an etiology was not identified, the findings may represent the effect of another variable such as concomitant immunosuppressive medication, or concurrent mild viral infection.

Importantly, the challenges with discerning drug toxicity in settings of pre-existing advanced liver disease from natural progression of liver disease should be recognized. From the perspective of labeling, the team is recommending clinical and hepatic laboratory monitoring during the treatment period, as clinically indicated. This language will be located in the LDV/SOF label section 8.7 Hepatic Impairment with cross reference provided in Adverse Reactions section 6.1. Further, postmarketing surveillance for the potential safety concern will be conducted as part of the ongoing safety surveillance for LDV/SOF and SOF in collaboration with OSE.

<u>Anemia</u>
Hemolytic anemia is a well-established toxicity of RBV and is viewed as a manageable toxicity with appropriate monitoring and by ribavirin dosage adjustments or blood

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transfusion if clinically necessary. With 12 weeks treatment, RBV discontinuation was observed in 8% of subjects in the groups with compensated cirrhosis or without cirrhosis, and 14% of subjects in groups with decompensated cirrhosis. Approximately 5% of subjects received blood transfusion, and the rate was generally comparable in the compensated cirrhosis (5%) and decompensated cirrhosis (4%) groups. No subjects discontinued LDV/SOF for anemia, and no exposure-response relationship for LDV/SOF was observed. Because anemia is a RBV-specific issue which is adequately addressed in the RBV label in Warning and Precautions, no specific labeling is being recommended for the LDV/SOF label at this time. Note that the review team is recommending language for careful clinical monitoring in decompensated patients as clinically indicated in the label section 8.7 Hepatic Impairment.

Cardiac events

Cardiac safety concerns were not identified in the SOLAR-1 and 2 trials. Overall, few cardiac events of interest were observed. Three bradycardia events were observed. The bradycardia events were in subjects who not taking concurrent amiodarone, the AEs did not lead to treatment discontinuation, and each AE was assessed by the investigator as unrelated to study treatment. Five cardiac failure AEs observed in the trials also did not result in treatment discontinuation and were confounded by an alternative plausible etiology or a pre-existing cardiac condition. A specific concern was not identified in analysis for coadministration with amiodarone, or coadministration with beta blockers and/or calcium channel blockers, or analysis of heart rate data. There are no new labeling recommendations based on findings in the SOLAR trials. There is ongoing postmarketing surveillance for bradycardia, cardiac failure and like events which is being performed by the LDV/SOF and SOF review teams in collaboration with OSE.

In other safety analysis of interest including renal events, pancreatitis, pancytopenia, dermatologic events, the identified cases were either confounded by use of an implicated medication or plausibly explained by another etiology; and we are not recommending new or additional labeling. No cases of suicide or rhabdomyolysis were observed. Lastly, there were no clinically meaningful differences in the safety profile across gender, race, and ages < or ≥ 65 years.

7.1 Methods

The safety of LDV/SOF was established previously in patients without cirrhosis or with compensated cirrhosis. The current supplements are intended to support labeling in two new populations: 1) patients with decompensated liver disease (i.e., CPT B or C), and 2) patients who are post-liver transplantation (i.e., fibrosis F0-F3, CPT A, B, C).

The SOLAR-1 and SOLAR-2 trials form the primary source of data. The SOLAR trials are open-label trials in which subjects are randomized to 12 weeks or 24 weeks of

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LDV/SOF + RBV treatment. The objective of the safety review is to characterize the safety profile in the new populations for the treatment durations, in order to allow an adequate benefit-risk assessment for the regulatory recommendation and decision.

The submissions include a summary of clinical safety, clinical study reports for both trials, electronic datasets, narratives summaries for deaths, transplant cases, SAEs, discontinuations due to AEs, and cases identified as potential DILI. The minutes from the IAC meetings were reviewed. The safety update report was also reviewed to identify additional concerns which emerged in the 60-day period following submission of the sNDAs. New postmarketing information submitted to the LDV/SOF IND or NDA during the sNDA review period were not independently reviewed by this clinical reviewer; however, the clinical review team was provided regular updates for any new safety-related information noted in postmarketing reports.

Safety analyses were performed with pooled data from SOLAR-1 and SOLAR-2 trials with analyses from the pooled datasets presented throughout this review (source, ISS or integrated summary of safety datasets in S007-009). Analyses were also performed using combined data from genotype 1 plus genotype 4 subjects who received at least one dose of treatment. The demographic and baseline disease characteristics for the combined genotype 1 plus 4 subjects are similar to characteristics described for genotype 1 subjects in section 6.1.2 of this review.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary sources of safety data for the current supplements S-007 to 009 are the SOLAR-1 and SOLAR-2 trials. Briefly, these are identically designed trials enrolling CHC subjects with either genotype 1 or 4 infection with decompensated cirrhosis; or post-liver transplantation without cirrhosis, with compensated cirrhosis, or with decompensated cirrhosis. Please refer to section 5.1 for trial details.

7.1.2 Categorization of Adverse Events

Adverse events were categorized using the Medical Dictionary for Regulatory Activities (MedDRA), Version 16.1. Treatment-emergent AEs were defined as events which began during the treatment period up to 30 days after discontinuation of all study agents, or pre-existing conditions with worsening severity or seriousness. The severity of AEs and laboratory abnormalities was assigned by the investigator and graded as Grade 1, 2, 3 or 4 using the Gilead Grading Scale for Severity of AEs and Laboratory Abnormalities. According to this scale, grade 1, 2, 3, and 4 AEs are mild, moderate, severe, and life-threatening, respectively.

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7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The SOLAR-1 and SOLAR-2 trials were identical in design and size; data from the two trials were pooled for an integrated analysis of safety.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 670 subjects received at least one dose treatment including 336 and 334 subjects in the 12 and 24 week treatment arms, respectively. Overall, the majority of subjects (94%) had completed the assigned duration of study treatment, 12 weeks (at least 84 days) or 24 weeks (at least 168 days).

The mean duration of exposure to LDV/SOF + RBV ranged between 11.6 to 12.2 weeks and 23.1 to 24.1 weeks for subjects randomized to receive 12 and 24 weeks of treatment, respectively. Please refer to the trial population demographics in section 6.1.2 of this review.

7.2.2 Explorations for Dose Response

Please refer to the clinical pharmacology and pharmacometrics review by Dr. Jeff Florian for dose response and exposure response analyses. In summary, a relationship of LDV or SOF exposure was not identified. Anemia and its relationship with RBV dose was thoroughly analyzed because a proportion of subjects required dose reduction or discontinuation. The findings are presented in section 7.3.5. The reader is also referred to the original LDV/SOF NDA and SOF NDA clinical pharmacology reviews for LDV and SOF dose response analysis, respectively.

7.2.3 Special Animal and/or In Vitro Testing

No new animal and/or in vitro testing is submitted with the current supplements.

7.2.4 Routine Clinical Testing

Routine clinical testing was performed at pre-specified regular intervals in both trials. Study visits and safety-related procedures were identical in the two trials. The key assessments are outlined in section 5.3 of the review.

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7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to the original LDV/SOF NDA clinical review for details of the metabolic, clearance, and interaction workup.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

At present, SOF is the only approved NS5B nucleotide polymerase inhibitor. The main toxicity concern with this agent is the potential for cardiac toxicity, specifically bradycardia. A detailed safety evaluation of pertinent cardiac disorders was conducted with this review.

Current U.S. approved HCV NS5A inhibitors include ombitasvir (as a component of Viekira Pak and Technivie), LDV, and daclatasvir (DCV). The most common adverse reactions observed with Viekira Pak treatment were nausea, pruritus and insomnia. For DCV, the most common adverse reactions observed with treatment of DCV plus SOF were headache, fatigue, nausea and diarrhea, events which are included in the current LDV/SOF label.

7.3 Major Safety Results

The following tables provide an overview summary of the AE profile in the trial populations. Because the stage of underlying liver disease can affect the AE profile, the compensated groups are displayed separately in Table 12, followed by decompensated groups in Table 13.

Posttransplant subjects without cirrhosis or with compensated cirrhosis
Focusing on the 12 weeks treatment arms in the pooled SOLAR-1 and 2 data, AEs regardless of causality or severity were observed in 95% of subjects. Nonfatal SAEs were reported in 14% of subjects. The majority of nonfatal SAEs were unrelated to treatment with treatment-related SAEs reported in only 2% of subjects. LDV/SOF treatment was discontinued in only 1% of subjects; while RBV was discontinued in proportionally more subjects, 7%. In general, the findings in the 24 week treatment arm were comparable to the 12 week treatment arm (less than 5% difference); the notable exception is the much higher rate of RBV discontinuation (12%) in the 24 week treatment arm compared to 12 weeks treatment (7%).

Table 12: Overview of AEs in posttransplant subjects without cirrhosis or with compensated cirrhosis, SOLAR-1 and 2 pooled

	Fibrosis F0-F3 and CPT A LDV/SOF+RBV N=330	
Subjects experiencing any:	12 weeks n=167	24 weeks n=163
At least one AE	159 (95%)	158 (97%)
Treatment-related AE	134 (80%)	136 (83%)
SAE	24 (14%)	29 (18%)
Treatment-related SAE	4 (2%)	6 (4%)
Deaths	3 (2%)	1 (1%)
Discontinued LDV/SOF due to AE	2 (1%)	3 (2%)
D/c RBV due to AE	13 (7%)	20 (12%)
Grade 3-4 AE	35 (21%)	42 (26%)
Treatment-related grade 3-4 AE	22 (13%)	25 (15%)

Source: ADAE, ADSL datasets SOLAR -1 and 2 ISS pooled

Subjects with decompensated liver disease irrespective of transplantation status

The overall trends observed in compensated subjects were maintained in the decompensated cirrhosis groups. As shown in Table 13 below, comparing CPT B and C subjects, proportionally more subjects with CPT C stage experienced SAEs including treatment-related SAEs, deaths, RBV discontinuation, and grade 3-4 AEs.

Table 13: Overview of AEs in subjects with decompensated cirrhosis, irrespective of transplantation status, SOLAR-1 and 2 pooled

	CPT B LDV/SOF+RBV		CPT C LDV/SOF+RBV	
Subjects experiencing any:	12 weeks N=106	24 weeks N=106	12 weeks N=56	24 weeks N=61
At least one AE	102 (96%)	101 (95%)	55 (98%)	60 (98%)
Treatment-related AE	73 (69%)	85 (80%)	38 (68%)	43 (70%)
SAE	17 (16%)	34 (32%)	22 (39%)	27 (44%)
Treatment-related SAE	1 (1%)	5 (5%)	2 (4%)	1 (2%)
Death	3 (3%)	4 (4%)	4 (7%)	5 (8%)
Discontinued LDV/SOF due to AE	3 (3%)	6 (6%)	1 (2%)	5 (8%)
D/c RBV due to AE	11 (10%)	19 (18%)	10 (18%)	17 (28%)
Grade 3-4 AE	14 (12%)	29 (27%)	18 (32%)	26 (43%)
Treatment-related grade 3-4AE	4 (4%)	13 (12%)	5 (9%)	10 (16%)

Source: ADAE, ADSL datasets SOLAR -1 and 2 ISS pooled

7.3.1 Deaths and Liver Transplantations

Deaths

A total of 20 treatment-emergent deaths (3%) were observed in the SOLAR-1 and SOLAR-2 trials. The cases were equally distributed in the 12 week and 24 week treatment arms with 10 deaths in each arm.

Of the 20 fatalities, 16 deaths (2%) were in subjects with decompensated disease. In 13 of 20 cases, sepsis and/or multiorgan failure occurred in the setting of complications of liver disease including variceal bleeding, ascites, spontaneous bacterial peritonitis (SBP), splenic vein thrombosis, superior mesenteric vein thrombosis, HCC, hepatic encephalopathy. In 4 of 20 cases, a cardiac etiology was the cause of death including myocardial infarction, cardiac arrest (2), and aortic dissection; the two subjects experiencing cardiac arrest were not taking amiodarone. In 2 separate cases, an infectious etiology was identified as the cause of death, namely PML and staphylococcal sepsis. In one separate case, liver graft rejection confirmed by histopathology was the cause of death. A tabular summary of the fatal cases is provided in the appendix 9.4.

None of the deaths were assessed by the investigators as related to study treatment. Separate assessments performed by the appointed IAC members also concluded the deaths were not attributed to LDV/SOF. I reviewed the individual narratives for the 20 death cases. I agree the deaths do not appear to be attributable to LDV/SOF toxicity; however, it should be noted that discerning natural progression of liver disease from drug toxicity is challenging in patients with advanced liver disease who are at an increased risk of complications due to cirrhosis.

In the SOLAR trials, an additional 10 deaths occurred 30 days after the end of study treatment; these events were assessed by the investigators as unrelated to study treatment. In the SUR, a total of five deaths were reported including two deaths in SOLAR trials and three deaths in subjects receiving LDV/SOF in the HCV-TARGET database. These five deaths reported in the SUR were assessed by the individual investigators as unrelated to study treatment. In the SOLAR trials, the causes of death were cardiac arrest occurring nine months after treatment completion (n=1), and subdural hematoma occurring 30 days after treatment completion (n=1). In the HCV-TARGET database, the reported causes of death were acute respiratory failure (n=1), coronary artery disease (n=1), and death (n=1).

In summary,

- Treatment-emergent deaths were observed in 3% of subjects in the SOLAR-1 and 2 trials. The primary causes of death were verified and appear appropriate.

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- The most frequent AEs leading to death were complications of advanced liver disease, infection, or a cardiovascular event.
- In my assessment, no deaths in the SOLAR-1 and 2 trials are plausibly attributable to LDV/SOF. In setting of pre-existing advanced liver disease, discerning natural progression of liver disease from drug toxicity is challenging because patients are at an increased risk of complications due to cirrhosis.

Liver transplantations

A total of 11 treatment-emergent liver transplantations (2%) occurred in the SOLAR-1 and 2 trials. Six additional transplantations occurred 30 days after the end of study treatment.

As expected, all subjects who underwent treatment-emergent liver transplantation had decompensated cirrhosis specifically with baseline CPT B (n=3) or CPT C (n=8) stage of liver disease. Subjects were transplanted because an appropriately matched organ had become available (n=6), or because the MELD scores increased in the setting of empyema (n=1), secondary to complications of paracentesis procedure (n=1), streptococcal bacteremia (n=1), and sepsis (n=1). One separate subject received a liver transplant to manage hemophilia and recurrent variceal bleeding, the hemophilia accompanying recurrent bleeding from portal hypertension made this case exceptional from the viewpoint of transplant. Patients with decompensated cirrhosis can develop worsening of MELD scores in response to infection, or other complications associated with portal hypertension. Independent assessments performed by the appointed IAC members concluded the transplants were not due to LDV/SOF. I agree with the IAC assessment that the transplants do not appear attributable to LDV/SOF. A tabular summary of treatment-emergent liver transplantations is provided in the appendix 9.4.

7.3.2 Nonfatal Serious Adverse Events

Overall, 127 of 670 subjects (19%) experienced at least one SAE. The majority of SAEs were considered by the investigator as unrelated to study treatment. In general, the SAEs appear to reflect complications of advanced liver disease or comorbidity consistent with the enrolled population. Treatment-related SAEs were observed in 19 (3%) subjects. Of the treatment-related SAEs, anemia attributed to RBV was the most frequently observed event. Excluding anemia-related SAEs, treatment-related SAEs were observed in seven subjects (1%) in SOLAR trials.

By liver disease stage, proportionally more subjects in the decompensated groups experienced an SAE compared to compensated groups. In decompensated groups, SAEs were observed in 24% and 36% with 12 and 24 weeks treatment, respectively;

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whereas in compensated groups SAEs were observed in 14% and 18% with 12 and 24 weeks treatment, respectively.

Treatment-related SAEs reported in at least two subjects were anemia (n=9), and hemolytic anemia (n=2). As shown in Table 14, the remaining treatment-related SAEs were reported in one subject each: vomiting, sinus arrhythmia, sick sinus syndrome, portal vein thrombosis, hyperbilirubinemia, hemoglobin decreased, fall, dyspnea, and diarrhea.

The SAEs of anemia, hemolytic anemia, and hemoglobin decreased were considered by the investigator to be related to RBV and not LDV/SOF, and noting that the RBV label carries Warning and Precautions statements for hemolytic anemia; these SAEs are not discussed further. The table below summarizes the treatment-related SAEs excluding anemia related SAEs. Seven subjects (1%) in the overall trials population reported a total of eight SAEs.

Table 14: Drug-related SAEs, SOLAR-1 and 2 pooled (excludes RBV-related anemia)

Group/Treatment duration	Preferred AE term	Treatment discontinuation	Toxicity grade	Onset (study day)	Resolved
Pre-transplant					
1: CPT B - 24 Weeks	Hyperbilirubinemia	Yes	3	141	No
2: CPT C -12 Weeks	Fall	No	2	85	Yes
Posttransplant					
3: F0-F3 - 24 Weeks	Diarrhea	No	3	40	Yes
4: CPT A - 12 Weeks	Portal vein thrombosis	No	2	15	No
4: CPT A - 24 Weeks	Sick sinus syndrome	No	3	77	Yes
4: CPT A - 24 Weeks	Sinus arrhythmia	No	3	77	Yes
5: CPT B - 24 Weeks	Vomiting	No	1	156	Yes
7: FCH - 24 Weeks	Dyspnea	No	2	86	Yes

Source: ADAE, ADSL datasets SOLAR -1 and 2 ISS pooled

Two cardiac SAEs, sick sinus syndrome and sinus arrhythmia occurred in the same subject [ID 0123-8430-75436]. The specific arrhythmia was tachy-brady syndrome; this case was reported previously to the LDV/SOF and SOF IND as part of a separate evaluation of cardiac bradycardia assessment. The case was reviewed previously and I refer you to Dr. Sarah Connelly's review for bradycardia in DARRTS for detailed assessment. Hyperbilirubinemia SAE was reviewed with other cases screened for DILI in section 7.3.5. The remaining SAEs listed in Table 14 did not result in treatment discontinuation; except portal vein thrombosis the event had resolved with continued study treatment.

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In summary, the majority of SAEs were considered to be unrelated to study treatment and appear to reflect complications of advanced liver disease or another underlying comorbidity consistent with the enrolled population. Treatment-related SAEs were observed in 19 (3%) subjects. Anemia and related AEs were the most frequent treatment-related SAEs and were attributed to RBV. Excluding anemia-related SAEs, treatment-related SAEs were observed in seven subjects (1%) in the SOLAR trials.

7.3.3 Dropouts and/or Discontinuations

Overall, 20 of 670 (3%) subjects discontinued LDV/SOF due to an AE. This includes 6 and 14 subjects in the 12 and 24 week treatment arms, respectively. Most subjects who discontinued due to an AE had decompensated cirrhosis (n=15), and the remaining subjects (n=5) had compensated cirrhosis or fibrosis only.

By SOC, the most frequently reported AEs in > 2 subjects belonged to the categories Gastrointestinal disorders (n=4), Infections and infestations (n=3), Respiratory disorders (n=3), and Vascular disorders (n=3). By preferred term, the most frequently reported AEs observed in ≥ 2 subjects were gastric hemorrhage or gastric varices hemorrhage (n=2), sepsis (n=2), hepatocellular carcinoma (n=2), dyspnea (n=2), and acute renal failure (n=2). The following remaining AEs were observed in one subject each: ALT increased, AST increased, aortic dissection, chest pain, convulsion, dehydration, diarrhea, Escherichia infection, hepatic encephalopathy, hepatic failure, hepatic hydrothorax, hyperbilirubinemia, hypotension, edema, peritoneal hemorrhage, shock, type 2 diabetes mellitus, and vomiting.

- The AEs sepsis, Escherichia infection, hypotension, shock appear to be secondary to serious infectious processes. Review of individual narratives indicates LDV/SOF + RBV treatment was discontinued because of multiorgan failure. Further, please note all treatment-emergent deaths were reviewed by the IAC and none were attributed to study treatment.

- The AEs gastric hemorrhage, gastric varices hemorrhage, hepatocellular carcinoma, peritoneal hemorrhage, edema, hepatic hydrothorax, dyspnea, and hepatic encephalopathy are well-known complications of advanced liver disease and not an unusual finding in the enrolled population. Review of individual narratives suggests the events manifested as part of the ongoing hepatic pathology, and the challenges with discerning a contribution of drug effect are acknowledged. The AE dyspnea is notable as it resulted in two subject discontinuations and both AEs were assessed by the two separate investigators as related to study treatment. The occurrence of dyspnea is not unusual in patients with decompensated cirrhosis who experience shifts in fluid balance resulting in ascites and pleural effusion. Because the RBV label carries a warning for pulmonary disorders including pulmonary function impairment and pneumonitis, and because dyspnea is not a flagged concern with LDV/SOF from

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previous clinical trial and postmarketing use, no new labeling is recommended at this time.

The finding of two AEs of acute renal failure are concerning and prompted an analysis for renal failure events presented in detail in section 7.3.5. The AEs of ALT increased, AST increased, and hyperbilirubinemia are discussed in DILI analysis in section 7.3.5. The convulsion AE is discussed in section 7.3.4 with other FDA designated serious medical events.

7.3.4 Significant Adverse Events

Analysis for other medically serious events, as qualified by FDA's Designated Medical Events was performed. The pre-defined designated terms include acute pancreatitis, acute respiratory failure, agranulocytosis, anaphylaxis or anaphylactoid reaction, aplastic anemia, blindness, bone marrow depression, deafness, disseminated intravascular coagulation (DIC), hemolytic anemia, liver failure, liver necrosis, liver transplant, pancytopenia, renal failure, seizure, Stevens-Johnson syndrome (SJS), torsades de pointes, toxic epidermal necrolysis, thrombotic thrombocytopenic purpura, and ventricular fibrillation.

Among these events, acute pancreatitis, hemolytic anemia, liver failure, liver transplant, pancytopenia, SJS, and renal failure are discussed in other sections as AEs of Special Interest (liver transplant in section 7.3.1, the remaining events are in section 7.3.5).

Other designated events observed in the SOLAR-1 and 2 trials are summarized below, followed by labeling recommendations.

- Convulsion AEs were observed in two subjects: Both AEs were assessed by the investigators as unrelated to the study treatment, and both events are potentially confounded by alternate explanations, namely, head injury and prior history of seizure.
    - In one subject in Group 2 (pre-transplant CPT C), seizures requiring intubation occurred on day 4 of study treatment in the context of head injury and subdural hematoma; LDV/SOF + RBV treatment was withheld temporarily during the acute hospitalization and re-started subsequently without recurrence.
    - In a second case in Group 5 (posttransplant CPT B), the subject had a remote history of seizures and was not receiving antiepileptic therapy. Seizure event occurred on day 82 of treatment and resulted in discontinuation of LDV/SOF + RBV.

At present, convulsion or seizures are not labeled events in the LDV/SOF or RBV package inserts. Because the above cases are confounded, the review team is not

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recommending labeling language at this time. Instead, we recommend surveillance for convulsions or seizure cases in postmarketing reports to ascertain the need for labeling.

- One AE of DIC was observed in one subject: DIC developed as part of complications including bacteremia and septic shock. The event was assessed by the investigator as unrelated to study treatment, and did not result in treatment discontinuation.

- Acute respiratory failure AE was observed in one subject: The event occurred on day 77 of treatment in the context of bilateral pneumonia due to Hemophilus influenza infection. The event was assessed by the investigator as unrelated to study treatment, did not result in treatment discontinuation.

- Deafness AEs were observed in two subjects: One subject, age 64 years, developed new onset mild hearing loss (grade 1); and a separate subject, age 62 years, developed worsening of pre-existing hearing loss (grade 3). The onset was days 77 and 100 of treatment. The grade 1 event was assessed by the investigator as unrelated to study treatment; while the grade 3 event was assessed as treatment-related by the investigator. In both cases, LDV/SOF + RBV treatment was continued through the assigned 12 week duration.

Deafness, DIC, and acute respiratory failure are not labeled events for LDV/SOF. No new labeling is recommended based on the above cases.

7.3.5 Submission Specific Primary Safety Concerns

The following specific safety concerns are presented in this section: DILI, cardiac safety, anemia, renal safety, pancreatitis, pancytopenia, dermatologic events, and rhabdomyolysis.

Drug induced liver injury

While DILI is not previously described with LDV/SOF use, this is a special concern in patients with decompensated cirrhosis who are at increased risk of developing complications from advanced liver disease. A comprehensive analysis plan was discussed in the pre-sNDA stage (details are in section 2.5 of this review). This section first provides an outline of the analysis approach, analysis findings, followed by conclusion and labeling recommendations.

1) Review approach for DILI analysis

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The hepatic safety analysis was devised specifically to allow screening and assessment of DILI in the trial population with decompensated cirrhosis and post-liver transplant patients. At the pre-NDA meeting, the Applicant, in consultation with IAC experts from the field of hepatology and liver transplantation proposed alternative approaches to identify potential cases of DILI (details in section 2.5). The final agreed-upon criteria to screen for potential DILI cases include both laboratory abnormalities of relevance, and important hepatic adverse events and fatalities, as shown below. Subjects receiving treatment-emergent liver transplants were included to capture DILI events which may result in transplantation. The IAC assessed cases meeting any of the above criteria and assigned each case in the following categories:

- Possibly related to study treatment
- Unlikely to be related to study treatment; a clear, alternative explanation is available
- Insufficient data to make a determination

Of note, the above-stated causality assessment scheme is not aligned with the standard DILI Network (DILIN) causality scoring system. The Applicant's justification for not using DILIN scoring and developing a revised scheme is acceptable. The IAC determined DILIN scoring was not directly applicable to the trial populations because DILIN scores are designed for patients without pre-existing liver disease and the SOLAR-1 and 2 population had pre-existing liver disease with multiple co-morbid conditions, and subjects especially posttransplant patients were receiving several concomitant medications which can confound DILI determination.

A total of 61 potential cases of DILI were identified and reviewed by the IAC. My analysis of the safety database identified five additional cases which met the above-mentioned criteria but were not included in the IAC listing because onset was two or 30 days after stopping the study treatment. These additional cases were reviewed by me and Dr. Poonam Mishra, and we concluded these additional cases were unlikely to be DILI.

2) <u>Findings in the DILI analysis</u>

Of the 61 cases which met DILI screening criteria, 11 cases were treatment-emergent liver transplants and 20 cases were fatal events. The fatal and transplant cases are discussed previously in section 7.3.1 – all cases were assessed by the investigator and the IAC as unlikely to be treatment-related. Of the remaining cases screened for DILI, two were hepatic failure SAEs, one case had met protocol-specified laboratory stopping criteria, and the rest were selected as they met the pre-defined direct bilirubin, ALT, or AST criteria for DILI screening, as shown in table 15.

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Table 15: Summary of cases which met DILI screening criteria

DILI screening criteria (*some subjects met > 1 criteria)	IAC assessment	Reviewer comment
Treatment-emergent liver transplant(n=11)	11/11 Unlikely	Agree with the IAC assessment
Treatment-emergent death (n=20)	20/20 Unlikely	Agree with the IAC assessment
Hepatic failure-related SAE (n=2)	1/1 Unlikely	Agree with the IAC assessment
Protocol-defined liver stopping criteria (n=1)	1/1 Possible DILI	Agree with the IAC
Direct bilirubin > 1 mg/dL from baseline (n=10)	1/10 Possible DILI; 6/10 Biliary pathology present - unlikely; 3/10 Other explanation present - unlikely.	Agree with the IAC assessment
ALT or AST > 2 x BL (n=4)	3/4 Transient fluctuation which resolved with continued treatment - unlikely; 1/4 Rejection of transplant – unlikely	Agree with the IAC assessment
ALT or AST > 3 x post baseline nadir (n=14)	2/14 Possible DILI; 8/14 Transient fluctuations - unlikely; 2/14 Alternative explanation present - unlikely; 1/14 Unconfirmed end of treatment value - unlikely; 1/14 Insufficient information	Agree with the IAC assessment

Source: ADAE, ADSL, ADLB datasets SOLAR-1 and 2, ISS

Possible DILI

Cases assessed as possible DILI by the IAC are briefly summarized below. The primary reviewer and Dr. Poonam Mishra agree with the IAC assessment of each case.

1) Abrupt increases in direct bilirubin, ALT, AST resulting in treatment discontinuation [ID 1305-76108]: A 70 year-old male in the pre-transplant cohort with CPT B cirrhosis with a history of varices, portal-systemic encephalopathy, and ascites developed a marked increase in direct bilirubin to 10.1 mg/dL at study week 20. This was accompanied by increase in ALT 104 IU/L and AST 119 IU/L. Ribavirin and LDV/SOF were discontinued. At post-treatment weeks 2 and 4, the ALT and AST had improved; however, direct bilirubin continued to remain elevated and improved with dialysis. The IAC concluded DILI could not be excluded given the lack of alternative explanation for the abrupt rise in direct bilirubin.

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2) DILI confounded by concurrent use of lamotrigine, treatment discontinuation, positive dechallenge [ID 3055-75304]: A 57-year-old male in the posttransplant cohort with F0-F3 stage of fibrosis developed new ALT and AST increase at week 6 of study. Notable increases in total bilirubin were not observed. The peak ALT and AST were 85 IU/L and 105 IU/L, respectively, at week 8. Lamotrigine was started on study week 8. The nadir ALT was 6 IU/L, and the subject met liver stopping criteria (ALT > 10 x nadir). Treatment with LDV/SOF, RBV, and lamotrigine was stopped. Improvement in ALT and AST was observed at post-treatment day 17, but subsequent increases were recorded on day 31. The IAC concluded the findings were consistent with possible DILI, but the causal agent could not be specifically determined.

   Comment: The lamotrigine package insert carries a Warning/Precautions statement for Hypersensitivity Reactions. Hepatic abnormalities may present as part of the reaction. ALT and AST increases are also labeled events for lamotrigine; however, these were observed rarely or infrequently in clinical trials. In light of the timing of onset of ALT and AST increases as well as resolution in relation to initiation and discontinuation of lamotrigine, I agree with the IAC that the causal agent cannot be definitely determined.

3) Positive dechallenge case [ID 2130-75139]: A 45-year-old male in the pre-transplant cohort with F0-F3 stage fibrosis developed ALT and AST increases at study week 12. On-treatment ALT and AST had improved from baseline until week 12 when ALT 129 IU/L and AST 78 IU/L were observed. Increase in direct bilirubin was not observed at this timepoint; in fact, total bilirubin decreased from prior range of 2.7-3.9 mg/dL to 0.4 mg/dL at week 12. The subject completed the assigned 12 week treatment and the abnormal values had resolved at the subsequent posttreatment visits. The IAC concluded that DILI could not be excluded (potential positive dechallenge). The IAC also considered laboratory sample switch as a possibility in light of the total bilirubin values while on RBV.

4) ALT and AST increases were observed at a single timepoint at study week 8 in a 54-year-old male in the posttransplant cohort with CPT B cirrhosis [ID 1043-76602]. The values improved spontaneously at week 12 without a change in treatment. The IAC concluded clinically non-significant DILI was a possible explanation.

Transient ALT, AST increase

Transient increases in ALT and AST which resolved with continued study treatment were observed in 11 posttransplant subjects (table 16). DILI cannot be excluded as no alternative etiology explained the finding in each case. As shown in the table below, the increase in ALT, AST had returned to baseline/nadir at the next visit approximately four weeks later. The peak ALT ranged from 17 to 222 IU/L. In 6 of 11 subjects, the increase occurred in the first four weeks of treatment initiation. At the time of the

increase, the HCV RNA was either below the LLOQ or trending down. Importantly, all subjects continued treatment and achieved SVR12. The IAC assessed the finding as unlikely DILI and of trivial clinical significance.

Table 16: Summary of posttransplant subjects with transient ALT, AST increase

#	Group	Screening criteria met	Nadir/BL ALT (IU/L, mg/dL)	Peak ALT (IU/L, mg/dL)	Study week	HCV VL at the same visit/s	SVR12 (Y/N)
1	F0-F3	ALT or AST > 3 x nadir	12	39	20	<LLOQ	Y
2	FCH	ALT or AST > 3 x nadir	7	40	8	<LLOQ	Y
3	F0-F3	ALT or AST > 3 x nadir	5	17	20	<LLOQ	Y
4	F0-F3	ALT or AST > 3 x nadir	40	121	2	<LLOQ	Y
5	CPT A	ALT or AST > 3 x nadir	11	45	2,4,8	307, 68,<LLOQ	Y
6	CPT A	ALT or AST > 3 x nadir	31	104	4	<LLOQ	Y
7	CPT A	ALT or AST > 3 x nadir	51	151	8	<LLOQ	Y
8	CPT A	ALT or AST > 3 x nadir	8	48	16	<LLOQ	Y
9	F0-F3	ALT or AST > 2 x BL	23	63	2	89 (↓)	Y
10	F0-F3	ALT or AST > 2 x BL	70	222	1	148 (↓)	Y
11	F0-F3	ALT or AST > 2 x BL	28	61	1	3820 (↓)	Y

Source: ADAE, ADSL, ADLB datasets SOLAR -1 and 2, ISS

The pattern observed in 11 subjects suggests a potential drug effect; therefore, the review team requested the Applicant to comment on the collective findings and labeling implication.

In response, the Applicant stated the cases were confounded by use of immunosuppressive therapies (all were posttransplant patients). The Applicant acknowledged the finding may represent transient or self-resolving DILI and noted these were isolated (single-time point) increases which were specifically assessed by the IAC to be of trivial clinical significance. The Applicant also stated alternative explanations that were not captured in the study records, such as mild intercurrent viral illness, and unreported over-the-counter or herbal medications. The Applicant's response is reasonable. The review team also notes the ALT or AST increases did not result in treatment discontinuation or require additional clinical management. Importantly, all subjects completed the assigned LDV/SOF treatment and attained SVR12. Therefore, no specific labeling based exclusively on these cases is recommended by the clinical review team.

3) Conclusion and labeling recommendation

In previous clinical trials and postmarketing assessments, DILI was not identified as a specific safety concern with the use of LDV/SOF. Some concern with RBV use may exist based on past reports with interferon plus RBV regimens in decompensated cirrhosis and HIV-coinfection, although the precise contribution of RBV is not known.

The SOLAR-1 and 2 trial findings do not raise a new concern for DILI. Four possible cases of DILI were confounded by the underlying hepatic disease and/or concurrent use of potentially hepatotoxic medication, and not attributed to study treatment by the IAC. In 11 separate cases, mild increases in ALT or AST from baseline or nadir were observed, without an associated rise in direct bilirubin. These ALT or AST increases were in posttransplant patients with compensated cirrhosis or without cirrhosis; the observed increases were transient, resolved without intervention, and were assessed by the IAC to be of trivial clinical significance. While an etiology was not identified, the findings may represent the effect of another variable such as concomitant immunosuppressive medication, concurrent mild viral infection.

Importantly, the challenges with discerning drug toxicity in settings of pre-existing advanced liver disease from natural progression of liver disease should be recognized. From the perspective of labeling, the team is recommending clinical and hepatic laboratory monitoring during the treatment period, as clinically indicated. This language will be located in the LDV/SOF label section 8.7 Hepatic Impairment with cross-reference link provided in Adverse Reactions section 6.1. Further, postmarketing surveillance for the potential safety concern will be conducted as part of the ongoing safety surveillance for LDV/SOF and SOF in collaboration with OSE.

Cardiac safety

Serious symptomatic bradycardia is reported with LDV/SOF use in patients taking amiodarone, particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease; and amiodarone coadministration is not recommended with LDV/SOF. In the SOLAR-1 and 2 trials, new cardiac safety concerns were not identified. Overall, cardiac events of interest were observed in few subjects; and most of the serious events occurred in settings of septicemia or hemodynamic deterioration secondary to complications of advanced liver disease and were confounded. No labeling recommendations are being made for cardiac events based on the SOLAR-1 and 2 trial findings. Postmarketing surveillance for cardiac events will continue to be performed as part of the ongoing cardiac safety surveillance for LDV/SOF and SOF in collaboration with OSE.

Below is the analysis of cardiac events of special interest including bradycardia, cardiac failure or cardiomyopathy, serious events in subjects coadministered amiodarone, and adverse events related to abnormal ECGs was performed. In addition, analysis of heart

rate data in groups receiving beta blockers and/or calcium channel blockers was performed to identify additional asymptomatic cases or trends.

Bradycardia

A total of three bradycardia AEs were observed in the SOLAR-1 and 2 trials. The AEs occurred in subjects not receiving amiodarone, were assessed by the investigators as unrelated to study treatment, and did not result in treatment discontinuation.

- One subject developed grade 1 bradycardia on day 1 of treatment which resolved with continued study treatment; assessed as unrelated to treatment
- One subject developed grade 1 atrioventricular block; which was noted at a pre-dose assessment prior to initiating LDV/SOF; the event was assessed as unrelated to treatment
- One subject developed grade 2 bradycardia on study day 104 in the setting of gastrointestinal bleeding, myocardial infarction, renal failure. The subject subsequently died and the cause of death was multiorgan failure.

A separate bradycardia event occurred as part of tachycardia-bradycardia syndrome. The tachycardia-bradycardia event was reported as sick sinus syndrome AE. This case was reported to the LDV/SOF and SOF IND by the Applicant as part of an ongoing bradycardia assessment; the case was previously reviewed by the LDV/SOF and SOF clinical review team.

Cardiac failure and cardiomyopathy

A total of five cardiac failure or cardiomyopathy AEs were observed. Of these, two cases were reported to the LDV/SOF or SOF IND previously by the Applicant as part of an ongoing assessment for cardiac events, and these cases will not be discussed further. Three separate AEs which were not reported to the LDV/SOF or SOF IND were reviewed. Each of the AEs were assessed by the investigator as not related to study treatment, each event had resolved, and other plausible etiology or a pre-existing cardiac condition was reported in each narrative, as summarized below. Overall, the individual and collective findings do not support the need for additional cardiac labeling for LDV/SOF.

- Cardiac failure diagnosed in setting of hypovolemia after gastrointestinal bleeding (n=1)
- Cardiac failure from fluid overload following the cessation of oral diuretic therapy; the event was considered as resolved by the investigator after diuretic therapy was reinstated (n=1)
- Cardiac failure in a subject with pre-existing QT prolongation (n=1)

Amiodarone use and serious AEs

A total of two subjects were identified who had used amiodarone during the treatment period. I reviewed the clinical course in submitted narratives because both cases were fatal events. In each case, the subject with decompensated cirrhosis developed documented bacteremia followed by clinical deterioration. In one subject, amiodarone

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was used briefly during hospitalization of sepsis to manage atrial fibrillation. In summary, no toxicity concerns were identified in review of cases where amiodarone was co-administered with LDV/SOF + RBV.

Other related analysis
The review of five AEs of abnormal ECG did not raise concern specific to bradycardia or cardiac failure. The Applicant conducted an additional analysis of AEs of interest in the first two weeks of initiating beta blocker or calcium channel blocker therapy. The AE of dizziness was observed in a similar proportion of subjects starting beta blocker and/or calcium channel blocker therapy; compared to the remaining subjects who did not start beta blocker and/or calcium channel blocker therapy. Given the pharmacologic action of beta blockers and calcium channel blockers, namely decreases in heart rate, decrease in cardiac output and peripheral vasodilation, dizziness is not an unexpected finding.

Analysis of heart rate data was performed to identify cases which were not captured in the bradycardia AE analysis, and to assess unusual trends between subgroups receiving beta blocker plus study treatment, calcium channel blocker plus study treatment, and those not receiving beta blocker or calcium channel blocker with study treatment. No unusual trends in low heart rate were observed. As stated previously, decreases in heart rate are an expected outcome with beta blocker use, and the results of heart rate analysis were interpreted in light of this background effect.

In conclusion, no labeling recommendations are being made for cardiac events based on the SOLAR-1 and 2 trial findings. Postmarketing surveillance for cardiac events of potential concern is ongoing as part of safety surveillance for LDV/SOF and SOF in collaboration with OSE.

Anemia

Hemolytic anemia is a well-established toxicity of RBV and is viewed as manageable event with appropriate monitoring and requiring RBV dose reduction and blood transfusions, if clinically indicated. The RBV package insert recommends the starting dose 1000-1200 mg/day for patients with compensated liver disease, and this dose was administered to compensated groups 3, 4 in SOLAR-1 and 2 trials. Patients with advanced and decompensated liver disease typically do not tolerate the full dose due to RBV-induced anemia and lower starting doses of 600 mg/day were administered to decompensated groups with CPT B or C.

The main findings in the analysis for anemia AEs and clinically significant decrease in hemoglobin (Hgb) are outlined below, followed by presentation of analyses performed for groups with compensated cirrhosis and decompensated cirrhosis:

- Clinically significant Hgb decrease to < 10 g/dL or < 8.5 g/dL were more frequent in compensated groups compared to the decompensated groups in part due to

the higher starting RBV dose (1000-1200 mg/day in compensated subjects compared to 600 mg/day in decompensated subjects).

- Fewer RBV discontinuations were observed in compensated groups (8%) compared to decompensated groups (14%). Approximately 5% of subjects received blood transfusion, and the rate was generally comparable in the compensated (5%) and decompensated (4%) groups.
- No subjects discontinued LDV/SOF for anemia, and no exposure-response relationship for LDV/SOF was observed.
- Because anemia is a RBV-specific issue which is adequately addressed in the RBV label in Warning and Precautions, no specific labeling is being recommended at this time. The recommended language in section 8.7 Hepatic Impairment of the LDV/SOF label for careful clinical monitoring as clinically indicated is sufficient.

Posttransplant subjects without cirrhosis or with compensated cirrhosis

Decrease in Hgb less than 10 g/dL were observed in a substantial proportion of subjects (40%-49%) with the 12 week treatment as shown in the table below. This reflects effects of both the higher RBV starting dose and lower GFR at baseline in posttransplant patients. Ribavirin discontinuation was, however, observed in a smaller proportion of subjects (7%-9%) with 12 weeks treatment. There were fewer RBV discontinuations in the 12 weeks treatment arm (7%-9%) compared to 24 weeks treatment (14%-16%).

Table 17: Anemia and decrease in Hgb analysis in posttransplant subjects without cirrhosis or compensated cirrhosis, SOLAR-1 and 2 pooled

	F0-F3, CPT A			
Group	All Posttransplant			
CPT class	F0-3	F0-3	A	A
Treatment duration	12 weeks	24 weeks	12 weeks	24 weeks
	n=107	N=105	n=60	N=58
RBV starting dose	1000 or 1200 mg		1000 or 1200 mg	
Mean GFR BL (ml/min)	63.2	68	65	67
Median decrease Hgb	-2.6	-2.2	-2.3	-1.8
Hgb < 10 g/dL post BL	52 (49%)	44 (42%)	24 (40%)	27 (47%)
Hgb < 8.5 g/dL post BL	20 (19%)	12 (11%)	10 (17%)	9 (16%)
Required transfusion	7 (7%)	3 (3%)	1 (2%)	5 (9%)
RBV dose reduced	59 (55%)	55 (52%)	25 (42%)	33 (57%)
RBV discontinued	10 (9%)	15 (14%)	4 (7%)	9 (16%)
Anemia AE	47 (44%)	46 (44%)	21 (35%)	24 (41%)

Source: ADAE, ADLB datasets SOLAR -1 and 2, ISS

Subjects with decompensated cirrhosis irrespective of transplantation status
In general, clinically significant decreases in Hgb (< 10 g/dL, or < 8.5 g/dL) were observed more frequently in Class C groups compared to Class B. Regarding the treatment duration 12 or 24 weeks, there were fewer RBV discontinuations in the 12 week treatment arms compared to 24 week treatment arms for each group, pre-transplant CPT B or C, or posttransplant CPT B or C.

Table 18: Anemia and decrease in Hgb analysis in subjects with decompensated cirrhosis irrespective of transplantation status, SOLAR-1 and 2 pooled

	CPT B and CPT C							
Group	Pre-Transplant				Posttransplant			
CPT class	B	B	C	C	B	B	C	C
	12 week	24 week	12 week	24 week	12 week	24 week	12 week	24 week
	n=58	N=57	n=48	N=52	n=48	N=49	n=8	N=9
RBV start dose	600 mg		600 mg		600 mg		600 mg	
Median decrease Hgb	-0.9	-0.9	-0.8	-0.4	-1.4	-1.5	-0.7	0.7
Hgb < 10 g/dL	6 (10%)	12(21%)	19(40%)	17(33%)	17(36%)	30(61%)	6 (75%)	5 (56%)
Hgb < 8.5 g/dL	1 (2%)	4 (7%)	6 (13%)	5 (10%)	5 (11%)	10(20%)	1 (13%)	1 (11%)
Blood transfusion	0	1 (2%)	4 (8%)	4 (7%)	3 (6%)	6 (12%)	0	0
RBV dose reduced	9 (16%)	14(25%)	13(27%)	1 (33%)	15(31%)	2 (45%)	5 (63%)	5 (56%)
RBV discontinued	1 (2%)	6 (11%)	7 (15%)	16(31%)	11(23%)	13(27%)	3 (38%)	2 (22%)
Anemia AE	4 (7%)	10(18%)	9 (19%)	20(39%)	15(31%)	22(45%)	5 (63%)	3 (33%)

Source: ADAE, ADLB datasets SOLAR -1 and 2, ISS

In light of the number of RBV discontinuations, particularly in decompensated cirrhosis, an additional analysis was performed to explore any impact of RBV discontinuation including the timing of discontinuation on SVR 12 rates. The analysis concluded no overall impact of RBV discontinuation on relapse rates. Please refer to section 6.1.7 of this review for details. The analysis was performed by Dr. Florian and readers are referred to his review for details of RBV use in the SOLAR-1 and 2 trials.

Renal safety

No dosage adjustment of LDV/SOF is required for patients with mild or moderate renal impairment. The safety and efficacy of LDV/SOF have not been established in patients with severe renal impairment with GFR less than 30 mL/min/1.73m^2 or end stage renal

disease requiring hemodialysis. Nephrotoxicity is not described with use of LDV/SOF in previous clinical trials in pre-transplant patients without cirrhosis or with compensated cirrhosis. Because acute renal failure SAEs were observed in more than 2 subjects in the pooled trial data, an analysis for all renal failure and acute renal failure events was performed. Based on the analysis presented below, no new labeling is recommended for renal failure or like events.

Treatment-emergent adverse events of renal failure or acute renal failure were analyzed. A total of 22 unique cases were identified (table 19). The events were more frequent in subjects with decompensated liver disease (15 subjects with CPT B or C, 7 subjects with either F0-F3 fibrosis or CPT A). Of the 22 AEs, 11 were either grade 3 or 4 events, and 9 were SAEs. Only 2 events resulted in discontinuation of study treatment, and 2 other events were assessed by the investigator as related to study treatment. Although fewer AEs were observed in the 12 week dose groups, the median time to onset of AEs was 60 days (1-139 days).

Table 19: Summary of renal failure AEs, SOLAR-1 and 2 pooled

	F0-F3 or CPT A		**Decompensated CPT B or C**			
	Posttransplant		Pre-transplant		Posttransplant	
	12 weeks (n=167)	24 weeks (n=163)	12 weeks (n=106)	24 weeks (n=109)	12 weeks (n=56)	24 weeks (n=58)
ARF or renal failure AE	3 (2%)	4 (2%)	0	6 (5%)	1 (2%)	8 (14%)
Grade 1-2	1 (1%)	2 (1%)	0	2 (2%)	0	6 (10%)
Grade 3	2 (1%)	2 (1%)	0	4 (4%)	1 (2%)	1 (2%)
Grade 4	0	0	0	0	0	1 (2%)
SAE	1 (1%)	2 (1%)	0	3 (3%)	1 (2%)	2 (3%)
Treatment-related	0	1 (1%)	0	0	0	1 (2%)
Discontinued LDV/SOF	0	0	0	1 (1%)	0	1 (2%)

Source: ADAE datasets SOLAR -1 and 2, ISS

Select narratives of grade 3-4 events, SAEs, AEs leading to treatment discontinuation, and those assessed as treatment-related were reviewed. In many cases, renal failure appeared to be secondary to another complication such as hemoperitoneum leading to hypotension or shock (n=2), acute respiratory failure from *Hemophilus influenza* pneumonia (n=1), initiation of ACE inhibitor/thiazide diuretic therapy (n=1), or hepatorenal syndrome (n=1). In two cases assessed by the investigator as drug-related, grade 1 or 2 increase in serum creatinine was observed.

- Grade 1 increase in one subject was observed concurrently with cholangitis; the abnormality resolved with continued study treatment.

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- In the second subject, baseline serum creatinine levels ranged from 1.3-1.4 mg/dL and increased to 1.5-1.6 mg/dL from week 12 through week 24; the values returned to the baseline range after treatment completion.

In analysis for grade 3-4 abnormalities in serum creatinine, only one additional case of was identified: This was a subject with grade 3 serum creatinine which developed in the setting of gram positive bacteremia and marked increase in MELD to 40, both being confounding factors (bacteremia may be associated with pre-renal failure, and increase in MELD suggests worsening hepatic function raising the possibility of hepatorenal syndrome).

Hepatorenal syndrome (HRS)
Hepatorenal syndrome is a known complication of portal hypertension which usually occurs in advanced cirrhosis. HRS was reported in two subjects in the SOLAR trials; both cases are confounded by other ongoing conditions which precludes the identification of drug toxicity.

- One subject in the posttransplant cohort with F0-F3 fibrosis developed persistent increase in serum creatinine which began on day 7 of study treatment. Per the case narrative, the assessment by the nephrology consult was acute on chronic kidney injury secondary to HRS or secondary to multiple thoracentesis.
- One additional subject was diagnosed with HRS on day 33 of study treatment. The subject was pre-transplant with CPT C at baseline. At the time of HRS event, the subject also developed other features of worsening hepatic decompensation such as massive ascites and melena resulting in death. The IAC attributed death to natural progression of underlying liver disease and assessed unlikely to be related to study treatment; refer to section 7.3.5 for discussion.

<u>Assessment and labeling recommendation</u>
Nephrotoxicity has not been observed with use of LDV/SOF in previous clinical trials in patients without cirrhosis or compensated cirrhosis. The cases of potential concern in SOLAR-1 and 2 are confounded by concurrent use of potentially nephrotoxic medications, thoracentesis or systemic infections which can cause shifts in fluid balance and renal function, or hepatorenal syndrome which not unexpected in patients with advanced liver disease. At this time, we are not recommending changes to the label.

<u>Pancytopenia</u>
Pancytopenia AEs were reported in two subjects in the pooled database. In both cases, the event does not appear related to LDV/SOF. There are no labeling recommendations.

- In one case, anemia and leukopenia on study day 27 were not accompanied by decrease from baseline in the platelet counts; therefore, the case did not meet definition of pancytopenia. This subject was posttransplant with F0-F3 fibrosis, and receiving mycophenolate mofetil. Leukopenia may be secondary to

Reference ID: 3878679

mycophenolate, and anemia secondary to RBV. The subject continued LDV/SOF + RBV treatment with resolution of the event.

- In the other case, pancytopenia was observed in a subject who was posttransplant with CPT C cirrhosis. The subject with low WBC count and platelet count at baseline (2.95 cells/mm3 and 63,000 cells/mm3 respectively) experienced RBV-related decrease in Hgb from baseline. The AE of pancytopenia was recorded; although, it should be noted that only anemia was treatment-emergent and anemia was attributed to RBV by the investigator. RBV was discontinued for the anemia event, and the subject completed LDV/SOF treatment.

Pancreatitis and asymptomatic increase in serum lipase
Among AEs related to pancreatitis, one even of acute pancreatitis was observed in the pooled data. The subject [3910-76462] was posttransplant with CPT A cirrhosis, and had a past medical history of pancreatitis. Acute pancreatitis was diagnosed on study day 48. The event was assessed by the investigator as unrelated to the study treatment. The event resolved with continued use of LDV/SOF and RBV.

Overall, transient and asymptomatic lipase elevations of greater than 3 x ULN were observed in 11 subjects (2%) treated with LDV/SOF+RBV for 12 weeks in the SOLAR trials. This frequency is similar to frequencies observed in the SIRIUS trial with use of LDV/SOF + RBV for 12 weeks.

Dermatologic events
Rash of any kind, angioedema, and drug eruption AEs were analyzed. These events were observed in 23 subjects. All AEs were either grade 1 or 2 in severity; none were SAEs, and no events led to LDV/SOF discontinuation. One subject discontinued RBV for the AE generalized rash which began 2 days after starting LDV/SOF + RBV; and the AE was assessed related to RBV. In 15 of 23 subjects, the AE was assessed related to study treatment. Rash is a labeled event for RBV when used with interferon; rash is also labeled for LDV/SOF. At this time, no additional labeling for LDV/SOF is warranted based on the SOLAR findings.

Suicide or Rhabdomyolysis events
No suicide AEs are reported in the pooled data. No AEs of rhabdomyolysis are reported. CPK was not measured in the SOLAR trials. There are no related labeling recommendations.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Frequent ADRs observed in at least 20% of subjects in any decompensated groups are presented in Table 20. The frequently observed ADRs are already labeled for LDV/SOF and/or RBV. While labeled, it should also be noted a higher frequency of individual ADRs is reported in decompensated groups compared to observations in previous LDV/SOF trials in less advanced liver disease where LDV/SOF was administered with or without RBV. The finding of similar types of ADRs across the trial populations is generally reassuring; and higher ADR rates in decompensated groups are confounded by underlying advanced liver disease which in itself may predispose to events such as fatigue or nausea. The events of anemia and pruritus are common with RBV use and labeled in the RBV package insert. Some ADRs were reported at higher frequency with the 24 week treatment duration compared to 12 week treatment although this was not a consistent trend for all ADRs.

Table 20: Frequent ADRs (≥ 20% subjects) in subjects with decompensated cirrhosis, irrespective of transplantation status, SOLAR-1 and 2 pooled

	Pre-transplant Decompensated				Posttransplant Decompensated			
CPT class	B	B	C	C	B	B	C	C
Treatment duration	12 week	24 week	12 week	24 week	12 week	24 week	12 week	24 week
	n=58	n=57	n=48	n=52	N=48	n=49	N=8	N=9
Fatigue	20 (34%)	19 (33%)	11 (23%)	13 (25%)	15 (31%)	15 (30%)	2 (25%)	0
Headache	13 (22%)	11 (19%)	10 (21%)	6 (12%)	4 (8%)	8 (16%)	2 (25%)	2 (22%)
Nausea	13 (22%)	10 (18%)	7 (15%)	10 (19%)	8 (17%)	4 (8%)	0	0
Anemia	4 (7%)	8 (14%)	8 (17%)	17 (33%)	12 (25%)	19 (39%)	4 (50%)	3 (33%)
Pruritus	2 (3%)	12 (21%)	9 (19%)	4 (8%)	2 (4%)	3 (6%)	9 (19%)	0

Source: ADAE dataset SOLAR -1 and 2, ISS

Common ADRs observed in at least 20% of subjects in the compensated groups are presented below in Table 21. Each of these is a labeled event for LDV/SOF or RBV.

Table 21: Frequent ADRs (≥ 20% subjects) in posttransplant subjects without cirrhosis or with compensated cirrhosis, SOLAR-1 and 2 pooled

CPT class	F0-F3 or CPT A	
Treatment duration	LDV/SOF + RBV 12 week	LDV/SOF + RBV 24 week
	n=167	N=163
Anemia	64 (38%)	69 (42%)
Fatigue	60 (36%)	56 (34%)
Headache	28 (17%)	35 (21%)

Source: ADAE dataset SOLAR -1 and 2, ISS

Specific labeling for new ADRs is not warranted based on SOLAR-1 and 2 trials. The safety profile observed is generally consistent with expected outcomes in patients with advanced liver disease or previously described ADRs for LDV/SOF and/or RBV.

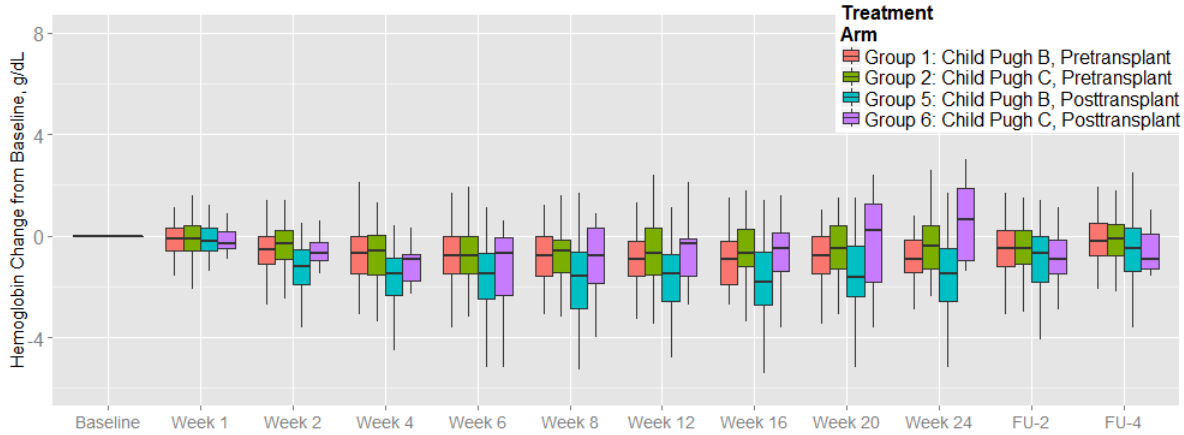
7.4.2 Laboratory Findings

Analysis of ALT, AST, direct bilirubin, serum creatinine, serum lipase, hemoglobin was discussed in relevant portions of section 7.3.5. Of the remaining laboratory parameters, no clinically significant trends were observed in analysis of platelet count, WBC count, absolute neutrophil count and the findings were generally consistent with expected findings in the enrolled population and/or RBV effects.

The figures below display change from baseline hemoglobin and change from baseline in platelet counts. For each parameter, data are presented for decompensated cirrhosis groups first followed by groups with compensated cirrhosis or without cirrhosis. The displays were prepared by Dr. Jeff Florian.

Reference ID: 3878679

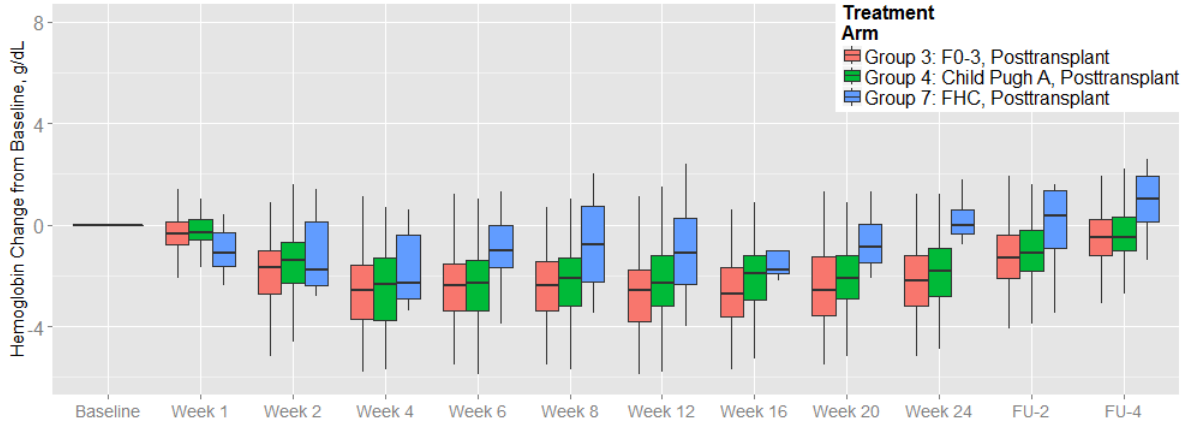
Hemoglobin: Median and interquartile change from baseline in hemoglobin versus visit for patients with decompensated cirrhosis from treatment Groups 1, 2, 5, and 6



	Baseline	Week 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	FU-2	FU-4
Group 1	115	114	114	114	110	112	105	53	54	48	103	101
Group 2	100	97	96	96	94	92	87	44	41	42	87	75
Group 5	97	95	95	95	94	92	88	45	45	41	90	77
Group 6	16	16	16	14	15	16	14	8	8	7	12	13

Number of patients

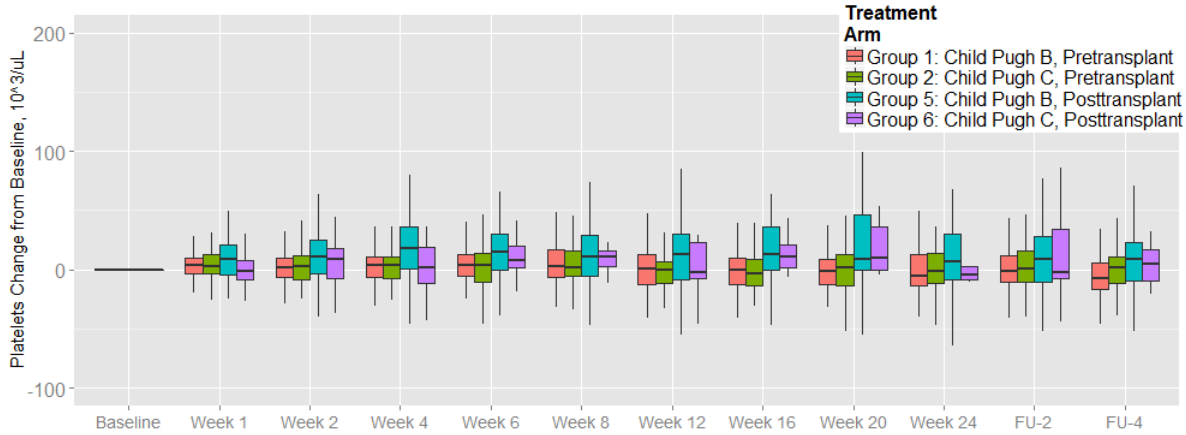
Hemoglobin: Median and interquartile change from baseline in hemoglobin versus visit for patients with compensated cirrhosis from treatment Groups 3, 4, and 7



	Baseline	Week 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	FU-2	FU-4
Group 3	212	208	204	210	204	205	198	99	99	97	200	169
Group 4	118	116	115	115	113	112	112	55	57	57	108	96
Group 7	11	11	10	11	9	11	11	4	4	4	10	9

Number of patients

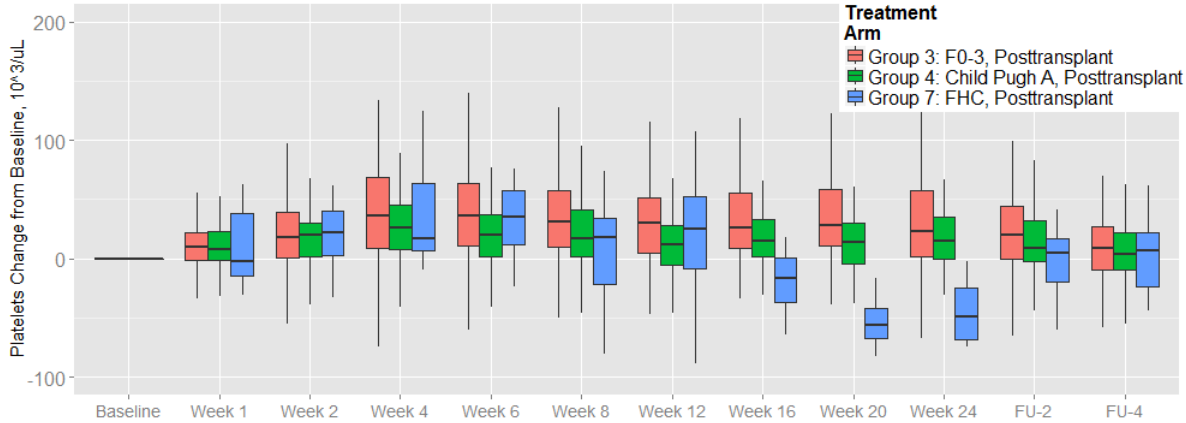
Platelet count: Median and interquartile change from baseline in platelets versus visit for patients with decompensated cirrhosis from treatment Groups 1, 2, 5, and 6



	Baseline	Week 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	FU-2	FU-4
Group 1	115	113	112	113	108	111	103	53	54	48	102	100
Group 2	99	94	89	92	87	88	84	43	38	40	86	73
Group 5	97	94	93	94	92	91	85	45	44	41	88	77
Group 6	16	16	16	14	14	16	14	7	7	6	11	13

Number of patients

Platelet count: Median and interquartile change from baseline in platelet versus visit for patients with compensated cirrhosis from treatment Groups 3, 4, and 7



	Baseline	Week 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	FU-2	FU-4
Group 3	211	207	201	209	203	204	196	99	94	97	198	167
Group 4	117	115	113	113	111	111	110	55	55	57	106	95
Group 7	11	11	10	11	9	11	11	4	4	4	10	9

Number of patients

7.4.3 Vital Signs

Analysis of changes in heart rate in the overall trial population as well as those receiving beta blocker or calcium channel blocker or agents in both classes was presented in Section 7.3.5 Cardiac Safety. No new safety concerns related to systolic or diastolic blood pressure or other vital sign parameters were identified to warrant labeling changes.

7.4.4 Electrocardiograms (ECGs)

Clinically significant abnormal ECGs are discussed in Section 7.3.5 Cardiac Safety.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies/clinical trials were conducted in support of this sNDA.

7.4.6 Immunogenicity

Immunogenic effects are not expected with LDV/SOF or RBV. A specific assessment was not performed for immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

An evaluation for dose-dependent AEs was not performed because only one dose of LDV/SOF, 90 mg/400 mg, was administered in the trials. This is the same dosage which is currently approved and marketed. Effects of the RBV dose on anemia are well described in the RBV label; and a specific evaluation of RBV dose and anemia was not performed.

7.5.2 Time Dependency for Adverse Events

The comparative safety profile with 12 and 24 weeks LDV/SOF + RBV treatment was discussed throughout sections 7.3 and 7.4. The Applicant had concluded no cumulative LDV/SOF dose effect with the longer 24 week treatment compared to the 12 week treatment course. The Applicant's findings were verified. With respect to RBV-induced anemia, a more pronounced decrease in hemoglobin were observed with 24 weeks dosing compared to 12 weeks dosing in Posttransplant decompensated groups as shown in section 7.3.5.

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7.5.3 Drug-Demographic Interactions

Analysis of the safety profile by gender, race, or age did not identify clinically meaningful findings, as summarized below.

By gender, no notable differences were observed in the proportion of AEs, discontinuations, treatment-related SAEs, or grade3-4 laboratory abnormalities between male and female subjects. In decompensated subjects (pre-transplant plus posttransplant), two AEs cough and pruritus were observed more frequently in female compared to male subjects (21% females versus 10% males, for each AE). Both AEs are labeled events for RBV, and not LDV/SOF.

By race, no meaningful differences in the safety profile were identified for Black versus Caucasian subjects; the finding should be interpreted cautiously as only 5% of enrolled subjects were Black. By age < or ≥ 65 years, no clinically meaningful differences in the safety profile were identified.

7.5.4 Drug-Disease Interactions

The overall safety profile of LDV/SOF in the SOLAR trials was generally consistent with the previously described profile in trials conducted in compensated liver disease patients who are pre-transplant. While the adverse event profile was more pronounced in patients with decompensated cirrhosis, this was attributed to the underlying clinical status or associated comorbidity or RBV toxicity, and an effect of LDV/SOF alone was not identified. The safety profile and differences observed across the compensated and decompensated liver disease groups are discussed throughout sections 7.3 and 7.4 of this review. For commonly occurring and clinically meaningful adverse events such as anemia, a thorough analysis of presentation across individual CPT stages A, B, and C is also presented.

No dose adjustment of LDV/SOF is recommended in patients with hepatic impairment. Dose adjustment for RBV is recommended in renal impairment as outlined in the RBV label. The LDV/SOF label provides reference to the RBV package insert for RBV dose adjustment instructions in renal impairment.

7.5.5 Drug-Drug Interactions

Important drug interactions for the trial-specific population include interactions between commonly immunosuppressive agents and LDV/SOF. In a drug interaction study in post-liver transplant CHC subjects, no clinically meaningful differences LDV or SOF PK was observed when LDV/SOF was co-administered with cyclosporine A-containing immunosuppressant regimen versus non-cyclosporine A-containing immunosuppressant regimens. Please refer to the clinical pharmacology/ pharmacometrics review by Dr. Florian for details.

7.6 Additional Safety Evaluations

No new concerns were identified in analyses assessing the risk of carcinogenicity, potential for LDV/SOF abuse, or overdose. The AE hepatocellular carcinoma was reported in 3 of 670 subjects (0.4%) in SOLAR-1 and 2 trials. (b) (4)

Regarding safety in pregnant participants, these populations were excluded from the SOLAR trials in light of RBV use. No pregnancies were reported in the SOLAR trials.

Pediatric trials are deferred and are being conducted as PREA PMRs.

7.7 Additional Submissions / Safety Issues

Information requested from the Applicant throughout the review period is incorporated in previous sections. Additional safety issues identified in this review are presented in previous sections.

8 Postmarket Experience

A review of all postmarketing adverse events in the FDA Adverse Event Reporting System (FAERS) was performed by the OSE/ DPV II. No new safety concerns were identified in the OSE/DPV II review of FAERS postmarketing reports of LDV/SOF use.

There were three cases of hypertensive crisis that support a drug-event association based on temporal association. One patient also experienced a subarachnoid hemorrhage. However, the cases were confounded by elevated BP at baseline and concomitant medications and comorbidities. A literature review did not find any published information supporting a relationship between SOF or SOF/LDV and hypertensive crisis or cerebral hemorrhage. Due to the small number of cases and the confounding factors, there is insufficient information to support a new safety signal. DPV II will continue to monitor for cases of hypertensive crisis and cerebral hemorrhage reported with SOF and SOF/LDV.

One case of pancreatitis with a temporal association to LDV/SOF was identified. However, the case was confounded by concomitant medications associated with pancreatitis. Due to only having a single case and the confounding factors, a definitive causal relationship between LDV/SOF and pancreatitis cannot be made at this time. DPV II will continue to monitor for all adverse events associated with the use of LDV/SOF. Please refer to the OSE pharmacovigilance review in DARRTS dated 12/4/2015 for details.

9 Appendices

9.1 Literature Review/References

Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA, 2011, A Sustained Virologic Response Reduces Risk of All-Cause Mortality in Patients With Hepatitis C. Clin Gastroenterol Hepatol, 9(6):509-516

Ghany, MG, Strader DB, Thomas DL, Seeff LB, 2009, Diagnosis, Management, and Treatment of Hepatitis C: An Update. Hepatology, 49(4):1335-1374

Kobayashi T, Hige S et al. Anemia and thrombocytosis induced by ribavirin monotherapy in patients with chronic hepatitis C. J Gastroenterol 2012 (47):1228–1237.

REBETOL Ribavirin package insert

van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, Heathcote EJ, Manns MP, Kuske L, Zeuzem S, Hofmann WP, de Knegt RJ, Hansen BE, Janssen HL 2012, Association between sustained virological response and allcause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA, 308(24):2584-2593

Veldt BJ, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, Manns MP, Hansen BE, Schalm SW, Janssen HL, 2007, Sustained Virologic Response and Clinical Outcomes in Patients With Chronic Hepatitis C and Advanced Fibrosis. Ann Intern Med, 147:677-684

9.2 Labeling Recommendations

Review of proposed labeling and related negotiations are ongoing at the time of completion of this review. Please refer to the CDTL memo by Dr. Poonam Mishra for the final labeling recommendations. The main revisions to the proposed labeling language are outlined below.

Section 1 Indications and Usage: is revised to include 'with or without ribavirin' because of the new recommendations of use with RBV for the new populations.

Section 2.1 Dosage and Recommendation: Revision of proposed dosing recommendation from text to table format.

Section 6.1 Adverse Reactions:

- Removal of statements referring to findings with 24 weeks dosing.

- Addition of the following statement describing deaths and transplants in decompensated subjects the SOLAR-1 and 2 trials

Among the 162 subjects with decompensated liver disease (pre- or post-transplant) who received HARVONI with RBV for 12 weeks, 7 (4%) subjects died , 4 (2%) subjects underwent liver transplantation, and 1 subject (<1%) underwent liver transplantation and died during treatment or within 30 days after discontinuation of treatment. Because these events occurred in patients with advanced liver disease who are at risk of progression of liver disease including liver failure and death, it is not possible to reliably assess the contribution of drug effect to outcomes. A total of 4 (2%) subjects permanently discontinued HARVONI due to an adverse event.

- Removal of proposed language about [redacted] (b) (4) .

Section 8.7 Hepatic Impairment: Inclusion of the following statement for patients with decompensated cirrhosis.

Clinical and hepatic laboratory monitoring, as clinically indicated, is recommended for patients with decompensated cirrhosis receiving treatment with HARVONI and ribavirin [see Adverse Reactions (6.1)].

Section 14 Clinical Trials:

- [redacted] (b) (4)

- Relocation of SVR12 response for FCH group 7 from table to text.

- Inclusion of relapse rates in the table format.

9.3 Advisory Committee Meeting

An advisory committee meeting was not held for the current supplements.

9.4 Tabular summaries of treatment-emergent deaths and liver transplants

Table 22: Summary of treatment-emergent deaths, SOLAR-1 and 2 trials

	Liver disease status/treatment arm (weeks)	Time to death (study day)	Cause of death (investigator assessment)	Pertinent information from case narrative
Compensated liver disease - posttransplant				
1	F0-F3/12 weeks	88	Liver failure due to chronic liver rejection	Graft rejection diagnosed by liver biopsy
2	CPTA/12 weeks	80	Progressive multifocal leukoencephalopathy	JC virus confirmed in cerebrospinal fluid
3	CPTA/12 weeks	110	Myocardial infarction (MI)	History of hypercholesterolemia, diabetes, hypertension
4	CPTA/12 weeks	171	Decompensated liver disease along with recurrent HCV	Multifactorial etiology including food poisoning, bacterial peritonitis, variceal bleeds
Decompensated liver disease groups				
Pre-transplant				
5	CPTB/24 weeks	57	Septic shock	Occurred in the setting of ongoing severe sepsis
6	CPTB/24 weeks	62	Cardiac arrest	Occurred in the setting of sepsis
7	CPTB/12 weeks	100	Sepsis and multiorgan failure	Ongoing pleural effusion, hepatic encephalopathy, supraventricular tachycardia
8	CPTC/12 weeks	67	Oliguric renal failure	Occurred in the setting of E. Coli infection, sepsis
9	CPTC/12 weeks	37	Multiorgan failure and septic shock	Occurred 15 days after liver transplantation surgery
10	CPTC/24 weeks	52	Septic shock	Occurred in the setting of recurrent bacterial peritonitis
11	CPTC/24 weeks	55	Gastrointestinal bleed and liver failure from HCV	Ongoing hepatorenal syndrome, melena, hemorrhagic esophagitis
12	CPTC/12 weeks	25	Staphylococcus aureus sepsis	Confirmed bacteremia progressed to sepsis
13	CPTC/24 weeks	26	Cardiac arrest	Probable ischemic event on autopsy
14	CPTC/24 weeks	124	Infiltrative multifocal hepatocarcinoma	
Posttransplant				
15	CPTB/12 weeks	59	Internal bleeding	Secondary to esophageal varices
16	CPTB/24 weeks	52	Cardiac	Dissection of thoracic aorta aneurysm
17	CPTB/24 weeks	76	Complications of cirrhosis	Occurred in the setting of sepsis, liver abscess, splenic vein thrombosis
18	CPTB/12 weeks	79	Cardiorespiratory arrest caused by ascitic decompensation (primary cause of death)	Initial hospitalization for ascitic decompensation, which progressed to hepatic encephalopathy, worsening renal function, respiratory insufficiency, death
19	CPTC/24 weeks	25	Massive intestinal ischemia	Superior mesenteric vein thrombosis, encephalopathy
20	CPTC/12 weeks	110	Liver cirrhosis due to recurrence of Hepatitis C virus following liver transplant in 2006	Initial hospitalization for bilateral community acquired pneumonia (H. influenzae), which progressed to respiratory failure, sepsis

Table 23: Summary of treatment-emergent liver transplants, SOLAR-1 and 2 trials

	CPT stage/ treatment arm	Approximate time on the transplant list relative to study day 1	Time on study treatment (days)	IAC assessment of DILI leading to transplant	Clinical context submitted in case narratives
1	CPT B/ 24 week	Enlisted on study day 7	157	Unlikely DILI	Hemophilia with multiple episodes of gastric variceal bleeds starting on study day 59. Liver transplant was considered curative for hemophilia; the GI bleeds influenced priority on the transplant list
2	CPT B/ 24 week	2 years prior	138	Unlikely DILI	MELD scores were improving on study treatment prior to transplant. Subject received a second transplant after the first graft failed
3	CPT B/ 24 week	4 years prior	79	Unlikely DILI	MELD scores were improving on study treatment prior to transplant
4	CPT C/ 12 week	Enlisted on study day 76	85	Unlikely DILI	Decline in liver function during hospitalization for empyema; subsequent diagnosis of anemia with worsening MELD
5	CPT C/ 12 week	1.8 years prior	84	Unlikely DILI	MELD scores were stable on treatment; transplanted because an appropriately matched organ was available
6	CPT C/ 12 week	1.5 years prior	77	Unlikely DILI	MELD scores were stable on treatment; transplanted because an appropriately matched organ was available
7	CPT C/ 12 week	1.5 years prior	21	Unlikely DILI	MELD scores increase to 40 at study week 1 in the setting of group B streptococcal bacteremia and recurrent *Clostridium difficile* infection. Subject received a liver transplant and died on posttransplant day 15 from septic shock and multiorgan failure
8	CPT C/ 24 week	1.5 years prior	91	Unlikely DILI	MELD scores were relatively stable; transplanted because an appropriately matched organ was available
9	CPT C/ 24 week	2 years prior	169	Unlikely DILI	MELD scores were stable on treatment; received liver donor transplant after approximately 2 years on the transplant list
10	CPT C/ 24 week	Enlisted on study day 6	80	Unlikely DILI	MELD scores were stable (18) until paracentesis procedure that was complicated by hemoperitoneum, hypotension, acute kidney insufficiency; MELD score increased to 32 and patient received a liver transplant
11	CPT C/ 24 week	8 months prior	95	Unlikely DILI	Patient developed sepsis and clinical deterioration including renal failure, with increase in MELD score and liver transplant

9.5 Financial Disclosure Template

Application Number: NDA 205834; supplements 7-9
Submission Date: 8/26/2015
Applicant: Gilead Sciences, Inc.
Product: Harvoni (ledipasvir and sofosbuvir tablets)

Reviewer: Charu Mullick MD
Date of Review: 01/04/2016
Covered Clinical Studies: GS-US-337-0123 (SOLAR-1), GS-US-337-0124 (SOLAR-2)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 403		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 21		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 19 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 2		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

The sponsor has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] No investigators are sponsor employees. A total of 21 investigators had disclosable financial interest including 19 investigators who received significant payments exceeding $25,000. This includes 11 principal investigators (PI) and 8 sub-investigators. An additional two investigators, one PI and one sub-investigator received equity interest over $ 50,000. For one sub-investigator, financial information was not obtained because the individual resigned from the study prior to

1 See http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf

Reference ID: 3878679

completion of the financial disclosure forms. Overall, 21 of 403 (5%) of investigators including PI and sub-investigators received significant payment or equity. A total of 157 participants were enrolled at the investigator sites representing 23% of enrolled participant in both trials. Most investigators were at U.S. sites. In the SOLAR-1 trial, 33% of the PIs had received payment and 36% of the trial participants were enrolled at their sites. Including sub-investigators, 40% of investigators had received payment or equity and they had enrolled 47% of participants in SOLAR-1. In contrast, only 1 investigator met the pre-specified criteria in SOLAR-2 and only 3% of the trial participants were enrolled at his site.

The primary endpoint for both trials is assessment of virologic outcomes, and the safety and tolerability of LDV/SOF plus ribavirin. Efficacy endpoints were determined objectively using laboratory results by (b) (4) and not expected to be vulnerable to bias on the part of the investigator. Laboratory related safety assessments were also performed by (b) (4) and not vulnerable to bias on part of the investigator. Adverse event reporting and relationship of events to study drug may be potentially vulnerable to bias. Additional sensitivity analyses for key efficacy and safety outcomes submitted upon Division request did not elucidate an impact of investigators receiving significant payments on the parameters.

While the SOLAR-1 and 2 trials are open-label and do not include an active or placebo control, the key endpoints for efficacy and safety rely on objective laboratory based parameters. The primary outcomes are therefore less likely to be subject to investigator bias. Additionally, LDV/SOF is already approved and its effect on SVR12 well-described in other populations with CHC disease. Further, the aforementioned sensitivity analyses conducted by the Applicant do not raise concern related to investigator bias. It should also be noted that one of the sites, for investigator Gregory Everson, was inspected by the FDA CDER Office of Scientific Investigation or OSI. The inspection did not identify concerning findings and the OSI concluded the data from this site was acceptable and may be used in support of the current application.

Trial	# Sites with PIs receiving significant payment or equity/# total sites (%)	# Subjects at sites with investigators receiving significant payment or equity /total number of subjects (%)
SOLAR-1	10/30 (33%) 12/30 (40%) including PI and sub-investigators	125/339 (36%) 147/339 (47%) including PI and sub-investigators
SOLAR-2	1/34 (3%)	10/334 (3%)
Pooled	13/64 (20%)	157/673 (23%)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHARU J MULLICK
01/27/2016

POONAM MISHRA
01/27/2016